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TRANSFUSION OF CONDITIONED UNIVERSAL BLOOD

CLINICAL OBSERVATIONS

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The practice of transfusing blood of group O (IV Moss) to persons belonging to any of the various blood groups is based on the assumption that cells of group O are not hemolyzed or agglutinated by any normal human plasma. The concept of a universal donor as developed by Ottenberg about thirty years ago has had considerable practical application, supported mainly on the theory that the dilution of a donor's blood and the absorption of the isoagglutinins anti-A and anti-B in a patient's plasma and tissue cells would tend to prevent any significant hemolysis or agglutination.

While some institutions with large transfusion services are using blood from universal donors without observing an undue reaction rate, hemolytic and other reactions have been reported after transfusion of such blood. They may vary through all degrees of severity, and a good number of representative cases have been reported in the literature. In an analysis by Gesse[1] in 1935 46 cases of hemolytic reaction were reviewed, of which 20 terminated fatally. Other authors have described severe and fatal reactions. The reports we are referring to do not include transfusion reactions caused by mistakes in determination of the blood groups because of technical errors or because of the presence of subgroups, such as A_2 and A_3, which had been overlooked. They may,

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1. Gresse, E. R.: Ueber die Verwendung des sogenannter Universalspenders bei der Bluttransfusion, Deutsche Ztschr. f. Chir. **245**:371, 1935. Hemolytic Shock After Blood Transfusion, editorial, J. A. M. A. **106**:2241 (June 27) 1936.

however, include a limited number of reactions which might have been caused by the newly discovered Rh factor. In some instances, laboratory work has demonstrated high isoagglutinin titers in a donor's blood. Many investigators attributed the cause of the reactions to the interaction between the potent isoantibodies of a donor's plasma and the group-specific components of the cells of a recipient. For this reason the titer of isoantibodies present in universal blood is frequently determined before a transfusion is given.

In this connection the state of New York has adopted an amendment to the Sanitary Code requiring the elimination of the so-called "dangerous" universal donor by such a procedure. Because of these various experiences with universal blood, most clinics today prefer the use of homologous blood for transfusions.

If the presence of high-titered isoantibodies in O blood constitutes the essential objection to the use of the universal blood, their partial or complete neutralization might be attempted. In previous publications [2] it has been shown that adequate reduction in content of isoagglutinins can be accomplished by the addition of small amounts of purified A and B specific substances. Universal blood conditioned in this manner may be considered "safe" from the standpoint of causing hemolysis or agglutination of a recipient's cells.

Because of the complexity of the clinical picture in most of the cases in which a transfusion is needed, a statistical evaluation of reactions to conditioned universal blood as against reactions to untreated O blood and homologous blood is difficult. It would seem that a statistical approach is possible only by comparison of groups of definite clinical entities with carefully selected control groups of similar nature, as the use of the isolated group-specific substances will only prevent reactions caused by the corresponding isoantibodies and not reactions due to other factors, such as those usually defined vaguely as "pyrogens." In other words, from a practical standpoint conditioned universal blood may be considered comparable to homologous blood. At the present time, it is possible to study the results of its use from the standpoint of efficacy of the method and its harmlessness.

As just mentioned, the problem consists in the reduction or elimination from a donor's blood of the anti-A and anti-B isoantibodies. This was accomplished by the addition to the O blood of the blood group–specific substances A and B. These two substances, which define the typing characteristics of all the cells in the body, including the erythro-

2. Witebsky, E.; Klendshoj, N. C., and Swanson, P.: Reduction or Elimination of the Anti-A Antibody in O Blood by Means of the Addition of the A Specific Substance, J. Infect. Dis. **67**:188 (Nov.-Dec.) 1940; Preparation and Transfusion of Safe Universal Blood, J. A. M. A. **116**:2654 (June 14) 1941.

cytes, have been made available in recent years. After the investigations of Freudenberg, Landsteiner [3] obtained the A specific substance from horse saliva, and Goebel [4] isolated this material from commercial peptones. Witebsky and Klendshoj [5] obtained an equally potent B substance from gastric juice. Briefly, the procedure of conditioning O blood is carried out as follows [6]:

Blood from a universal donor is collected for transfusion in a vacuum container in the usual manner. This blood may be used immediately, but most specimens are stored in the blood bank. In either case, the A and B substances in physiologic solution of sodium chloride are injected into the blood in the vacuum container and mixed gently for a few minutes before the transfusion is given. Initially, 25 mg. of A substance and 10 mg. of B substance were used arbitrarily in each 500 cc. of O blood. Later, it was found that smaller amounts could be used effectively.[7] There has been no demonstrable harm in using larger quantities, and the attempts to reduce the amounts are being made as a matter of economy. Lower limits have not yet been determined. More A substance than B substance has been used, as the anti-A titer is often found to be higher than the anti-B titer in the same blood. It is of importance that the addition of blood group–specific substances to normal human serum containing the corresponding isoagglutinins does not result in precipitation.

The effect of the group-specific substances has been determined by a comparison of the anti-A and the anti-B titer in each specimen before and after conditioning of the O blood. There is no standardized procedure for the determination of agglutinin titer which permits values from our laboratory to be compared with those of other investigators. The readings reported in this paper were obtained after centrifugation of the tubes and observation of the degree of agglutination macroscopically.

Before we proceed toward a detailed analysis of cases to be presented in this report, the following 2 cases of emergency transfusion may be cited to illustrate the general procedure:

Case 1.—A steam shovel operator, B. F., aged 56, was accidentally pinned within the cabin of his machine. He was cut free with the aid of torches and

3. Landsteiner, K.: Note on the Group-Specific Substance of Horse Saliva, Science **76**:351 (Oct. 14) 1932.

4. Goebel, W. F.: The Isolation of the Blood Group A Specific Substance from Commercial Peptone, J. Exper. Med. **68**:221 (Aug. 1) 1938.

5. Witebsky, E., and Klendshoj, N. C.: The Isolation of the Blood Group-Specific B Substance, J. Exper. Med. **72**:663 (Dec.) 1940.

6. In our hospital intravenous therapy, including blood transfusions, is given by members of the department of anesthesia. Dr. Paul Searles, the head of this department, cooperated with us.

7. Part of this material was prepared and made available to us by Eli Lilly & Co.

brought to the hospital in shock. His pulse was rapid and thready. The blood pressure was 54 systolic and 30 diastolic, and his abdomen was rigid. Without blood typing or cross matching, he was given 500 cc. of group O blood with A and B substances added. His blood pressure had increased to 106 systolic and 74 diastolic after the completion of the transfusion. No reactions from the transfusion were observed. He subsequently received 500 cc. of plasma, followed by 1,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride. The patient was later found to belong to group O, but nevertheless, it is interesting that the transfused O blood had the following high anti-A and anti-B agglutinin titers: anti-A equal to 1:256; anti-B equal to 1:64. After the addition of the A and B specific substances, these titers were determined to be 1:4 for the anti-A isoagglutinins and 1:2 for the anti-B isoagglutinins. The anti-A titer would definitely be considered high. Had the recipient belonged to group A, a serious reaction might have occurred with the use of this blood. The A substance lowered the titer to insignificance.

CASE 2.—The hospital was notified by a private physician that a patient, M. B., whom he had just delivered at home was having a massive postpartum hemorrhage, and a house physician was sent out immediately in the ambulance equipped with a transfusion set and 500 cc. of group O blood to which the A and B substances had been added. The mother was found to be in shock with a low blood pressure and thready pulse. Without typing or cross matching, the prepared blood was infused while the hemorrhage was brought under control. The response was rapid. The estimated blood loss was 1,500 cc. The recipient was never typed. The universal donor's blood was found to contain an anti-A titer of 1:128, which was reduced to 1:2, and an anti-B titer of 1:32, which was reduced to zero. No reaction occurred.

REVIEW OF CASES

In the present series of cases a total number of 176 transfusions were given to 147 patients. For twenty-four hours following the completion of a transfusion each patient was under close observation for any subjective or objective signs of reactions, particularly chills, rises in temperature or pulse rate, icterus and hemoglobinuria. The two last-named manifestations were not observed in any case.

Of the total number of transfusions, 123 were given without any observable changes in the patients. The remaining 53 transfusions represent the number to be subjected to analysis. It is impossible to establish criteria which in very ill patients would permit accurate differentiation between reactions to the transfused blood and similar signs due to the illness itself. Perhaps the tabulation of temperature rises over a short period, such as two hours, might tend to exclude, to some degree, the chance rise resulting from the disease, but reliable statistics cannot be based on such arbitrary limits. In each case we have endeavored to evaluate temperature rises over a twenty-four hour period, and we have attributed them to surgical procedures or infectious processes, unless the general temperature pattern of the patient seemed to have undergone a definite change following transfusion.

A total number of 39 transfusions were given which were accompanied by a rise in temperature during the following twenty-four hours and in which we attributed the fever to the patient's general condition and not to the transfusion. These 39 transfusions were given to 34 patients. Increases in temperature were not associated with chills in any case, and in no instance did a significant part of the temperature increase take place during the first two hours following the transfusion. During this period temperature and pulse were recorded every fifteen minutes.

In 24 of these transfusions either the recipient's temperature did not exceed 101 F. at any time during the twenty-four hour period following the transfusion or the difference between the recorded temperature at the

Maximum Rise in Temperature in the Twenty-Four Hours Following Transfusion of Conditioned Universal Blood

Blood Group	Case No.	Maximum Temperature Increase, F.	Diagnosis
A	6	2	Amputation of leg; ascending infection
	7	2	Acute appendicitis with perforation
B	8	4.4 and 5.6	Postoperative appendical abscess with septicemia; infection of urinary tract and subcutaneous abscess
	9	3.4	Perforated ulcer; diffuse peritonitis
	10	5	Anterior and posterior colporrhaphy and amputation of cervix
	11	1.6	Abscess of abdominal wall
O	12	2.4	Diffuse peritonitis following appendectomy
	13	3.8	Acute cholecystitis after operation; postoperative bronchopneumonia
	14	3	Hysterectomy
	15	4.6	Removal of retroperitoneal tumor
	16	3	Gastric resection; linitis plastica
	17	1.8	Thyroid "storm"
	18	3.8	Gastric resection for adenocarcinoma; atelectasis; obstructive biliary cirrhosis
AB	19	1.4	Postoperative diffuse toxic condition of thyroid

beginning of the transfusion and the maximum temperature during the following twenty-four hours was less than 1 degree (F.). We feel that these transfusions need no further discussion. The remaining 15 transfusions were given to 14 patients who represented the greatest part of the acutely ill patients among the 34 just mentioned. To illustrate the pathologic conditions encountered in these 14 patients, we have tabulated the diagnosis along with the maximum temperature increase over the twenty-four hour post-transfusion period. In 1 case (8) the patient received 2 transfusions, and the increases in temperature in both instances are indicated in the table. These temperature peaks were occurring daily before the patient received his first transfusion and continued for many days after the last transfusion, and they were typical of the fever curve generally seen in this type of infection of the urinary tract.

After deducting from the total the number of cases in which no reaction occurred, in addition to those in which we felt augmented temperatures were part of the normal course of events, there remained 10 cases in which the 14 reactions observed seemed unquestionably to have been precipitated by transfusion. Of these 10 cases, the patients in 5 belonged to blood group A, in 4 to group O and in 1 to group B. It may be stated again that in none of the cases did we observe signs of agglutination or hemolysis. The severity of the temperature reactions had the following distribution: Four transfusions produced temperature increases of between 2 and 4 degrees (F.); in 10 transfusions, the increase exceeded 4 degrees (F.) and chills were present. In the 39 transfusions mentioned previously temperature rises were not associated with chills, while in these 14 transfusions, temperature rises with chills occurred in about two thirds. In all the cases in this group with 1 exception the patients had received multiple transfusions prior to the infusion of universal blood treated with the group-specific substances, and in a number of these cases the transfusions with conditioned universal blood were specifically requested by the attending clinicians as a result of previously encountered reactions.

In cases in which chills occurred during an infusion period the transfusion was stopped immediately. As a rule this took place after the administration of 200 to 300 cc. of blood. In general, the types of reaction which we definitely consider as a direct result of the transfusions were similar in nature, chiefly consisting in increases in temperature and pulse, with associated chills in 10 of the 14 transfusions. It is likely that these reactions were mainly caused by pyrogens. Recent investigations have shown that it is possible to reduce the number of such reactions considerably by eliminating all possible sources of contamination from the transfusion equipment. Rather than to review all details of these 10 cases, it seems desirable to report the following cases to illustrate our general observations:

Case 3.—A 19 year old girl, R. A., was admitted to the hospital with a six months' history of abdominal cramps and bloody diarrhea. Previous treatment in another hospital had included repeated transfusions. A diagnosis of nonspecific ulcerative colitis was confirmed by roentgen examination, and patchy ulceration was seen through the sigmoidoscope. Her red cell count was 4,100,000, with 76 per cent hemoglobin, and her white cell count was normal. Marked improvement occurred after ileostomy.

The patient's supportive treatment consisted in a number of transfusions and intravenous infusions of sulfanilamide solutions. She was found to belong to group O. Her first transfusion in this hospital caused a chill, a temperature rise of 5.2 degrees (F.) and a pulse rise of 10 after the administration of 250 cc. of homologous O blood without the A and B substances. On each of the following two days she received sulfanilamide solutions intravenously, resulting in temperature increases of 2 and 3 degrees (F.), respectively, and corresponding pulse increases of 30 and

15. One day later she received 500 cc. of universal blood treated with the A and B specific substances, which produced a temperature rise of 2 degrees (F.) but no increase in pulse. She experienced itching of the skin after this transfusion. Three subsequent transfusions without the use of the group-specific substances on three consecutive days gave rises in temperature of 2, 3.5 and 3.2 degrees (F.). Pulse rates remained unchanged. The 3.5 degree rise was associated with a chill.

This case illustrates a typical reaction to transfusions. The neutralization of the isoantibodies in the one specimen of blood treated with group-specific substances would not be of any significance, as the corresponding group-specific antigens, A and B, were not present in the recipient's cells, and there is, of course, no advantage in conditioning universal donor blood if the blood is given to a group O recipient. The conditioning of universal donor blood when given to a group O recipient in our procedure is a matter of routine and not a matter of necessity. The case also affords a demonstration of the similar types of reactions which may follow intravenous infusions of substances other than blood.

CASE 4.—A patient, N. R., was admitted to another Buffalo hospital immediately after hematemesis. Previous history indicated the presence of a peptic ulcer. He had a blood pressure of 80 systolic and 40 diastolic; his pulse rate was 58 per minute, and his temperature was 96.4 F. He belonged to group B. Immediately following admission his red cell count was 4,030,000, with 84 per cent hemoglobin. Five days later the count had dropped to 2,490,000, with 48 per cent hemoglobin. At that time he received 500 cc. of homologous blood, which produced a chill, a temperature rise of 4.2 degrees (F.) and a pulse rise of 30. Two days later the transfusion was repeated with 500 cc. of universal blood neutralized with the A and B substances. This transfusion resulted in a similar reaction. Again the temperature rose 4.2 degrees (F.), with a chill, and the increase in pulse rate was 46. No further complications occurred, and the patient recovered. The anti-A titer in the donor's blood was reduced from 1:16 to 1:2, and the anti-B titer, from 1:8 to zero.

There is a striking similarity in the reactions to the two transfusions. Whatever the explanation is, the isoantibodies may not be considered as offenders, as the titers after neutralization were insignificant, and even the original titers were low enough to place the donor in the low-titered universal group.

The following case is added because it is the only one in which a severe transfusion reaction occurred after the first transfusion using universal blood conditioned with the A and B substances. This case serves as a further illustration of the freakish reaction picture often encountered in multiple transfusions.

CASE 5.—A 36 year old Negress, P. H., had been admitted to the hospital with a bleeding cervical neoplasm. Biopsy had revealed a squamous cell carcinoma, and radium had been implanted. Six months later metastasis had developed. Her red cell count was 2,700,000, with 62 per cent hemoglobin. A severe infection of the urinary tract and rapid loss of weight soon terminated in death. During her last

admission she received 3 transfusions after it had been determined that she belonged to group A. The first transfusion consisted of 500 cc. of universal blood conditioned by the addition of the A and B substances. She reacted with a temperature increase of 2.8 degrees (F.), a chill and a pulse rise of 10. Her next transfusion ten days later, for which homologous blood in the same amount was used, resulted in a temperature rise of 4 degrees (F.) without chill, and a pulse rise of 35. The last infusion of 500 cc. of homologous blood five days later did not cause any reaction.

The universal blood used in the first transfusion had an anti-A titer of 1:256, which was reduced to 1:2. The anti-B titer was 1:128, which was also reduced to 1:2. Ordinarily, the anti-A titer would be considered sufficiently high to be unsafe for transfusion, and this would be particularly true in a patient exhibiting a marked degree of anemia. Although a reaction occurred following this transfusion, no signs ascribable to hemolysis or agglutination appeared.

The question arises as to the possible sensitization in human beings by the preparation used for the conditioning of O blood. Such sensitization might manifest itself if subsequent transfusions would follow the first transfusion after a certain interval. We had several cases in which we gave multiple transfusions of blood containing the A and B substances without observing any trace of clinical sensitization. In some instances we intentionally tried to create optimal conditions for sensitization by allowing an interval of one to three weeks to occur between the first and the second transfusion, without any manifestation of sensitization.

COMMENT

The advantages of routine use of universal blood for transfusions cannot be disputed. However, severe and fatal reactions have been reported by a number of investigators as the result of the indiscriminate use of O blood, particularly in cases in which large amounts have been transfused and in which marked anemia was present in the recipients. The danger considered inherent in the use of universal blood is commonly ascribed to the high content of isoantibodies capable of causing hemolysis and agglutination of the recipient's cells—the basis of the term dangerous universal donor.

The method used in the cases reported obviates this danger by partial or complete neutralization of the isoagglutinins with the corresponding purified group-specific substances A and B. It cannot be stressed too much that this procedure can be expected to accomplish just that and that reactions due to other factors will occur from transfusion of such conditioned universal blood as frequently as they are encountered after the use of homologous blood. In the specimens of blood used for transfusions in the cases reported, the average anti-A agglutinin titer was found to be 1:100 and the corresponding anti-B titer

was 1:74. Treatment with A and B specific substances reduced these figures to 1:3 for the anti-A agglutinins and 1:4 for the anti-B agglutinins.

During the practical performance of the reported transfusions a number of points have presented themselves which it seems desirable to discuss. To begin with, we were somewhat apprehensive as to our ability to keep our blood bank sufficiently supplied by O donors. However, our experiences indicate that a cooperative house staff is perfectly capable of procuring an adequate number of universal donors at all times. Our prospective donors are typed immediately when they present themselves to the hospital, and those belonging to group O are selected. The determination of the blood group is done by mixing potent test serum of group A and of group B with the cell suspension under investigation. If an O blood is found, the serum of the donor prepared routinely for serodiagnosis of syphilis is rechecked against known A cells and B cells, which are invariably agglutinated by serum of group O. From the standpoint of economical and efficient operation of the blood bank, it is important that the method described permits us to supply the various hospital services with adequate amounts of blood from a smaller "stock," inasmuch as all the blood available can be used.

Careful judgment should permit one to manage an O blood bank without waste. Another advantageous consequence is that blood may be transfused in a fresher state, as the turnover of the total stock of blood is much more rapid.

The use of conditioned universal blood does away with typing and cross matching as emergency procedures. If universal blood is properly selected and the isoantibodies reduced in strength to within safe limits by the addition of the A and B specific substances, such blood may be given to any recipient without typing and cross matching in an emergency. The only exception to that rule is found in the rare cases of pregnancy in which isoimmunization might have produced an Rh or a similar antibody. In these cases a special type of blood characterized by the absence of the Rh factor is required. We do not advocate the abolishment of cross matching as a routine procedure when it can be done at the leisure of the laboratory personnel, since such a procedure contributes a definite additional safeguard against mistakes.

We have emphasized the use of conditioned universal blood as part of the operation of blood banks, which are now available in most larger hospitals. It is our belief that the use of conditioned universal blood will simplify a blood bank system sufficiently to permit its use in small hospitals. If selection of donors is not an emergency procedure, suitable donors may be determined in small communities by having their blood

typed in qualified laboratories at any distance. Universal donors designated in this manner may contribute their blood to the local blood bank or in individual cases at any time as most desirable.

It is entirely beyond the scope of this paper to discuss the relative merits of transfusion of plasma and of whole blood. When plasma is produced from large pools of blood, the average residual agglutinin titers are likely to be relatively low. If plasma is produced on a small scale from individual specimens of blood, the same considerations may apply as to O blood, and high agglutinin titers can be reduced by the addition of the blood group–specific substances.

SUMMARY

Clinical observations on the transfusion of O blood conditioned by the addition of the A and B specific substances are reported. Such blood is characterized by extremely low isoantibody titers and combines the advantages of O blood in regard to the absence of group-specific factors in the cells with the absence of the isoantibodies in the fluid of AB blood.

No reactions ascribable to the combination of transfused isoantibodies with the A and B specific substances of the recipient were observed in 176 transfusions. The A-B mixture used was found to be effective and harmless.

The advantages of the procedure and its relation to the operation of a blood bank with O blood predominantly or exclusively are discussed. Typing of a patient can be eliminated, an important time-saving factor in emergencies. By adopting the method described, it becomes possible for smaller hospitals to maintain a blood bank with O blood exclusively and thus avoid difficulties in keeping blood of all four groups available.

Conditioned universal blood may be kept ready and immediately available for any civil or war emergency.

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REFRACTORY HEMOLYTIC ANEMIA

A REPORT OF FIVE CASES IN WHICH TREATMENT WAS WITH SPLENECTOMY

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During the past four years we have been puzzled as to the basic cause and exact classification of a hemolytic type of anemia which we have observed in 5 adults. Furthermore, we were unable to influence the clinical course either by conservative medical treatment or by more radical surgical therapy. Detailed observations have been made in each case before, during and after splenectomy, and we have had the opportunity of making postmortem examinations in 3 cases. Because of the unusual clinicopathologic syndrome, we wish to present our observations and attempt a brief review of the literature and the rather confusing ideas on the subject.

REPORT OF CASES

CASE 1.—M. H., a white housewife aged 58, was admitted to the University of Nebraska Hospital March 12, 1938 and discharged May 29. For approximately three months before admission the patient had noticed a gradual loss of weight associated with weakness and followed shortly by a "yellow color" of the skin. After the appearance of the jaundice, she had noted anorexia, dizziness and several attacks of nausea and vomiting without colicky pain. She had, however, been subject to mild recurrent epigastric distress following meals, especially after eating fried food. For one month prior to admission she had been aware of some numbness of her fingers but had not noted glossitis or paresthesias of the lower extremities. Though the urine had been dark since the onset of the jaundice, she had not noted any "clay-colored" stools. The past history was nonessential. The family history was entirely irrelevant with regard to any similar disease. While the patient was in the hospital we had the opportunity to study samples of blood from her 2 brothers and 1 sister. There was no evidence of anemia, reticulocytosis, latent jaundice or increased fragility of the red cells.

On physical examination the patient appeared slightly undernourished, with a definite icteric tint to the skin and scleras. A few small hemangiomas were scattered generally over the skin, but no petechiae were present. The eyes, ears and nose were normal. A number of teeth were carious. The tongue was slightly coated but without evidence of papillary atrophy. There was no generalized enlargement of the lymph nodes. Though the heart was not enlarged, a soft

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systolic murmur was heard over the mitral area; the blood pressure was 150 systolic and 72 diastolic. The lungs were clear. The abdomen was not remarkable except that the edge of the liver was palpable 5 cm. below the right costal margin and the spleen was moderately enlarged. The neurologic examination revealed nothing abnormal.

Laboratory examination yielded the following data: The blood count showed a hemoglobin content of 3.9 Gm. per hundred cubic centimeters (23 per cent), 1,200,000 erythrocytes and 2,800 leukocytes, with 23 per cent segmented polymorphonuclears, 1 per cent basophils, 52 per cent lymphocytes and 14 per cent monocytes. The smear showed marked variation in size and shape of the red cells, with a predominance of macrocytes; no spherocytes were seen. Marked polychromasia was apparent, and a few normoblasts were found. The hematocrit determinations showed a mean corpuscular volume of 129 cubic microns, a mean corpuscular hemoglobin content of 44 micromicrograms and a mean corpuscular hemoglobin concentration of 34 per cent. The percentage of reticulocytes was 71.6. The fragility test of the red cells showed beginning hemolysis at 0.46 per cent and complete hemolysis at 0.28 per cent. The bleeding and clotting times were normal; the platelets numbered 284,000. The icterus index of the blood was 55 units. The van den Bergh reaction was direct, positive and immediate, with a quantitative result of 40 mg. per liter. The reaction for urobilinogen in the urine was positive in a dilution of 1:200. The stools gave a negative reaction for occult blood. Analysis of gastric contents showed 14 degrees of free hydrochloric acid and 87 degrees of total acid. The Wassermann reaction of the blood was negative.

Roentgen studies of the gastrointestinal tract failed to show any organic lesions. Studies of the gallbladder showed only a fair concentration of dye with several irregular shadows of negative density lying within the gallbladder, which were interpreted as calculi. Roentgenograms of the long bones showed no gross evidence of any pathologic condition which could account for the anemia.

For three weeks the patient was given large oral and parenteral doses of liver and iron, alone and in combination, without appreciable beneficial effect on the blood count. During this interval the temperature ranged from 99 to 100 F. and the pulse rate from 90 to 100 per minute. The degree of jaundice remained about the same. Since iron and liver were ineffective, they were discontinued, and seven transfusions totaling 3,235 cc. of blood were given during the next two weeks. The blood counts during this interval ranged from 3.4 to 6.8 Gm. of hemoglobin per hundred cubic centimeters, 660,000 to 1,800,000 red cells and 5,200 to 8,000 white cells. The differential count continued to show the same pattern as on admission. The percenatge of reticulocytes varied from 80 to 90. The icterus index continued to fluctuate between 40 and 55 units. The hematocrit determinations showed the same macrocytic tendency.

Because the patient failed to respond to active medical treatment, splenectomy was performed April 20, with the patient under spinal anesthesia. The spleen after removal weighed 552 Gm. Except for slight hepatic enlargement and the presence of cholelithiasis, no significant pathologic evidence was found to account for the persistent hemolytic anemia. After operation the patient had an uneventful clinical convalescence. However, the blood count failed to respond to splenectomy in any way comparable to that seen in patients with familial hemolytic jaundice.[1]

1. Sharpe, J. C.; McLaughlin, C. W., Jr., and Cunningham, R.: Hemolytic Jaundice: Immediate and Delayed Changes in the Blood After Splenectomy, Arch. Int. Med. **64**:268-279 (Aug.) 1939.

Therefore, four additional transfusions totaling 1,680 cc. of blood were given during the five weeks following operation. When the patient was dismissed from the hospital five weeks after splenectomy, the blood count showed a hemoglobin content of 8 Gm. per hundred cubic centimeters (47 per cent), 2,600,000 red cells and 10,600 white cells. Reticulocytosis (66 per cent) was still evident. The icterus index was 25 units. Though the patient remained moderately jaundiced, she felt rather definitely improved in general strength.

The patient returned to the outpatient department on Feb. 8, 1939, ten months after removal of the spleen. She still complained of persistent weakness. The hemoglobin content was 8.6 Gm. per hundred cubic centimeters (51 per cent); the red cell count, 2,120,000, and the white cell count, 9,100, with 55 per cent segmented forms, 16 per cent staff forms, 20 per cent lymphocytes, 4 per cent basophils and 5 per cent monocytes. The blood smear showed occasional Howell-Jolly bodies, rare nucleated red cells, moderate anisocytosis, marked polychromatophilia with basophilic stippling and achromia. No spherocytes were seen in the smear. Hematocrit determinations showed a mean corpuscular volume of 143 cubic microns, a mean corpuscular hemoglobin content of 40.5 micromicrograms and a mean corpuscular hemoglobin concentration of 28.3 per cent. The icterus index of the blood was 19 units. The platelets numbered 720,000. The percentage of reticulocytes was 24. The erythrocyte fragility test showed beginning hemolysis at 0.52 per cent and complete hemolysis at 0.28 per cent.

Thirteen months after splenectomy the patient's family physician reported she had gained in strength and weight, but that her anemia persisted. The hemoglobin content was 12.7 Gm. per hundred cubic centimeters (75 per cent); the erythrocyte count, 3,750,000, and the leukocyte count, 7,500.

Pathologic Observations.—The spleen weighed 552 Gm. It was of essentially normal shape, and the cut surface showed nothing particularly unusual.

Sections show trabeculae approximately normally arranged. The lymphoid follicles are few in number and are small, usually without reaction centers. There is extensive pigmentation. Part of this pigment lies within the phagocytes, but some seems to lie free in the intercellular spaces. The sinusoids contain numerous large phagocytes, and there is occasional red cell phagocytosis. Reticulum cells are proliferating, and their differentiation can be followed to the production of free phagocytes. Scattered through the tissue are large numbers of polymorphonuclear neutrophils. These are all relatively mature. Eosinophils are present in moderate numbers. Nucleated red cells are present in large numbers. These are frequently arranged in clusters which show varying stages of maturity.

Bone marrow obtained by sternal aspiration was studied before and after operation. Before operation 78 per cent of the nucleated forms in the bone marrow were normoblasts. After operation the percentage of normoblasts decreased to 43, with a corresponding rise in the more mature forms of neutrophils. No abnormal cell forms were encountered.

Case 2.—E. M., a married white woman aged 60, entered the University of Nebraska Hospital Nov. 29, 1936 and was dismissed Jan. 19, 1937. For three months prior to admission the patient had complained of epigastric distress associated with periodic attacks of nausea, vomiting, progressive weakness and a loss of 25 to 30 pounds (11 to 14 Kg.) in weight. The patient had been studied in the outpatient department, and a tentative diagnosis of carcinoma of the stomach had been made. She was placed on oral iron and liver therapy, without beneficial

effect. The patient stated she had not had any previous illness of a serious nature, and the family history was noncontributory with regard to any similar disease.

On physical examination the patient presented slight pallor and icterus of the skin. The temperature and the pulse and respiration rates were normal. The eyes, ears, nose and throat were normal. There was no generalized lymphadenopathy. The lungs were clear. The heart was normal except for a slight systolic murmur at the apex; the blood pressure was 108 systolic and 70 diastolic. The abdomen was pendulous, with a large ventral hernia. In addition, a large mass was present in the upper left quadrant of the abdomen which extended from the xyphoid process to a point 5 cm. below the umbilicus and which was interpreted as the spleen. Neither the pelvic examination nor the neurologic examination revealed anything abnormal.

The blood count showed a hemoglobin content of 11.9 Gm. per hundred cubic centimeters (70 per cent), with 4,650,000 red cells and 2,800 white cells. The differential count showed 48 per cent segmented forms, 10 per cent staff forms, 40 per cent lymphocytes and 2 per cent monocytes. The percentage of reticulocytes varied from 0.1 to 0.4 per cent. The fragility test of the red cells showed beginning hemolysis at 0.44 per cent and complete hemolysis at 0.26 per cent. Hematocrit studies revealed a mean corpuscular volume of 77 cubic microns, a mean corpuscular hemoglobin content of 23 micromicrograms and a mean corpuscular hemoglobin concentration of 30 per cent. The icterus index of the blood was 16 units, and the van den Bergh reaction was direct and immediate. The reaction for urobilinogen in the urine was positive in a 1:40 dilution. The stools were highly colored with bile, yet the reaction for occult blood was negative. The bleeding time was two minutes, and the clotting time, eighteen minutes. The platelets on several examinations ranged from 104,000 to 238,000. Both the galactose tolerance and the bromsulphalein tests for hepatic function yielded normal results. Analysis of gastric contents disclosed a normal amount of free hydrochloric acid.

Roentgenograms of the gallbladder were interpreted as giving evidence of cholecystitis with cholelithiasis. Roentgen studies of the gastrointestinal tract showed a large mass in the left upper quadrant of the abdomen that extended from the diaphragm to the iliac crest, which was interpreted as an enlarged spleen. A pneumoperitoneum was produced by injecting 2,200 cc. of carbon dioxide into the peritoneal cavity. The mass was easily visualized and again was interpreted as an enlarged spleen.

One month after admission to the hospital splenectomy was performed by Dr. Herbert Davis with the patient under general anesthesia. The spleen, weighing 1,700 Gm., was found to be covered with adhesions and was removed with difficulty. The liver was grossly normal in appearance, whereas the gallbladder was adherent and thickened and contained calculi. After the operation a transfusion of 500 cc. of whole blood was given. The patient had an uneventful convalescence and was dismissed from the hospital on the twenty-first day after operation, at which time the blood count showed a hemoglobin content of 11.7 Gm. per hundred cubic centimeters (69 per cent), 4,300,000 red cells and 12,300 white cells. At this time the percentage of reticulocytes was 0.5; the icterus index was 16; the bleeding and clotting times were normal; the platelets numbered 324,000, and the hematocrit reading and the results of the fragility test were essentially the same as on admission.

The patient was readmitted to the hospital Feb. 26, 1938, approximately one year later, complaining of severe recurrent pains in the upper right quadrant of the abdomen associated with jaundice. These attacks were interpreted as typical

of obstructive cholelithiasis. Except for these episodes of pain, her general condition had apparently improved. The results of physical examination were not essentially different from those of the previous examination. The hemoglobin content was 14.6 Gm. per hundred cubic centimeters (86 per cent); the erythrocyte count, 4,950,000, and the leukocyte count, 10,100. The differential count was within normal limits. The percentage of reticulocytes was 2.2. The icterus index was 10 units, and the van den Bergh reaction was direct. The platelet count and the bleeding and coagulation times were normal.

Cholecystectomy was performed on March 4, at which time marked technical difficulty was encountered because of the amount of adhesions around the gallbladder and a rather marked tendency to bleeding. Though the patient's immediate postoperative course was uneventful, during the following six weeks she underwent several severe internal hemorrhages, accompanied by profound shock, and required four blood transfusions. Persistent postoperative hemorrhage finally led to death on April 19.

Pathologic Observations.—The spleen weighed 1,700 Gm. It was normal in gross contour. The section shows numerous well formed lymphoid follicles, usually with definite reaction centers. Eosinophils are present in considerable numbers. There is appreciable reticulum cell proliferation, with the formation of many free phagocytes within the sinusoids, but there is no accumulation into definite collections. Occasional normoblasts are seen, but no erythropoietic fossae are encountered. No phagocytosis of red cells is seen.

Autopsy.—Death occurred sixteen months after splenectomy and shortly after cholecystectomy. External examination showed a sinus tract in the right upper quadrant of the abdomen penetrating it deeply and communicating with the gallbladder bed and the common duct region. This was walled off from the general peritoneal cavity by relatively firm adhesions. The heart, lungs and gastrointestinal tract generally were normal in appearance except for the presence of a considerable amount of fresh and partly digested blood in the small bowel. The cystic artery opened into the bottom of the sinus tract, as did the common bile duct. This permitted the escape of blood into the gastrointestinal tract. The liver was rather soft, and sections showed extensive fatty degeneration. The lymph nodes from several areas showed no abnormalities. No studies of the bone marrow were done.

Case 3.—M. B., a housemaid aged 25, entered the University of Nebraska Hospital for the third time Nov. 30, 1936, with symptoms of a severe crisis of hemolytic anemia. On the two previous admissions, four years before, she had been in similar crises with a red cell count of about 1,000,000. Symptoms of increasing weakness, yellowish pallor and bouts of diarrhea had been present for two months.

On physical examination the patient was extremely pale and moderately jaundiced. The temperature was 101.6 F.; the pulse rate, 120 per minute, and the blood pressure, 108 systolic and 62 diastolic. There were no purpuric manifestations on the skin, and the flicking test gave a negative result. There was no glossitis or papillary atrophy of the tongue. Generalized lymphadenopathy was absent. There were no pulmonary abnormalities. There was a soft systolic murmur at the apex. The spleen was enlarged and was palpable 4 cm. below the left costal margin. The neurologic examination revealed nothing abnormal.

At the time of admission the hemoglobin content was 3.4 Gm. per hundred cubic centimeters (20 per cent); the erythrocyte count, 990,000, and the leukocyte count, 4,000. Except for a shift to the left of the polymorphonuclear series, the

differential count was normal. The blood smear showed extreme variation in the size and shape of the red cells, with numerous polychromatophilic cells, Cabot rings and Howell-Jolly bodies. The mean corpuscular volume of the erythrocytes was 103 cubic microns; the mean corpuscular hemoglobin content was 36 micromicrograms. The bleeding, clotting and clot retraction times were normal; the number of platelets was slightly reduced. The percentage of reticulocytes was 5.5. The fragility test of the red cells showed beginning hemolysis at 0.46 per cent and complete hemolysis at 0.28 per cent. The icterus index was 27 units; the van den Bergh reaction was indirect, with a quantitative result of 2 mg. per liter. The reaction for urobilinogen in the urine was positive in a dilution of 1:60. There was complete absence of free hydrochloric acid in the gastric contents, and examination of the stool did not reveal any blood. The urine was normal, and the Wassermann reaction of the blood was negative. A biopsy of the bone marrow showed marked hyperplasia of the erythropoietic tissue. Roentgenograms of the skull showed definite evidence of increased thickness.

The patient was critically ill. Emergency splenectomy was considered, but transfusions were elected in view of the extremely low blood counts and the poor operative risk. A transfusion of 450 cc. of whole blood by the indirect citrate method was given on each of two successive days. Though there was no immediate febrile reaction after either transfusion, a few hours after the second one the patient complained of severe abdominal pain. The jaundice became more intense, and the spleen became tender and increased in size. The temperature gradually rose to 105.4 F. During the next twenty-four hours the erythrocyte count dropped from 1,700,000 to 1,360,000 and the hemoglobin concentration from 36 to 25 per cent. The donor and recipient bloods were rematched and found to be compatible. The patient was watched carefully for signs of renal damage, but no anuria, hematuria or hemoglobinuria developed. Four days later splenectomy was performed with the patient under gas-ether anesthesia, with prompt improvement in the blood and progressive decrease of the jaundice. Two months later the gallbladder was removed because of cholelithiasis. The patient was discharged from the hospital in a greatly improved state, both clinically and hematologically.

The patient reported for a check-up examination one year after splenectomy, at which time she felt moderately improved. There were still a definite pallor and mild icterus of the skin. The hemoglobin content at this time was 7.82 Gm. per hundred cubic centimeters (46 per cent); the red cell count, 2,630,000, and the white cell count, 13,100. The differential smear was normal. The percentage of reticulocytes was 8.7. The erythrocyte fragility test showed beginning hemolysis at 0.56 per cent and complete hemolysis at 0.20 per cent. Though we have had no further opportunity personally to study the patient in detail, she recently reported from her home on the west coast that she has continued to have spells of poor health and fatigue, in spite of persistent oral and parenteral liver and iron therapy. Her last blood count, in June 1940, three and one-half years after splenectomy, showed a hemoglobin content of 11.90 Gm. per hundred cubic centimeters (70 per cent), 4,000,000 erythrocytes and 11,000 leukocytes, with 52 per cent polymorphonuclears, 47 per cent lymphocytes and 1 per cent eosinophils.

Pathologic Observations.—The spleen weighed 960 Gm. and was normal in shape. The cut surface showed rather extensive yellow stippling.

On section the lymphoid follicles are small and rather widely spaced, and only a few show definite reaction centers. There is considerable hyperplasia of

reticular cells, and stages of differentiation to the development of free phagocytes within the sinusoids can be traced. These phagocytes occur in numerous collections of three to thirty cells each. The individual cells are somewhat variable in size and shape, but all show large vesicular nuclei with chromatin arranged in fine strands and peripheral granules. The cytoplasm is moderate in amount, is finely granular and frequently contains pigment. Occasional cells have included erythrocytes. Eosinophils are numerous throughout the section. Normoblasts appear in considerable numbers, and there are scattered small erythropoietic centers.

Study of bone marrow obtained by sternal aspiration before operation showed approximately 50 per cent of the nucleated forms to be normoblasts. Shortly after operation the proportion was the same. Approximately one year after splenectomy a third aspiration showed approximately 30 per cent normoblasts, with a proportionate increase in neutrophils. No abnormal cells were encountered in any of these studies.

CASE 4.—J. L., a white man aged 62, was admitted to the University of Nebraska Hospital Oct. 21, 1936 and died November 30. The patient had first noticed the onset of undue fatigue one and one-half years before admission to the hospital. This weakness had become progressively more pronounced and was associated with a gradual loss of 37 pounds (17 Kg.) in weight. For about two months he had been aware of vague abdominal distress, which was partially relieved by lying down. He had not been conscious of any abdominal mass until his physician had discovered it some ten days prior to his admission to the hospital. The family history was noncontributory, and the patient's past history was nonessential.

On physical examination the patient appeared to be in a fair state of general nutrition. Except for slight icterus of the scleras, the color was good. The eyes, ears, nose and throat were not remarkable. The heart and lungs were normal for a man of his years. The abdominal examination showed a large mass extending from just under the left costal margin down to and below the umbilicus. The edge of the liver was palpable 2 fingerbreadths below the right costal margin, smooth and not tender. Except for an indirect inguinal hernia on the right side, no other significant physical abnormality was found.

The laboratory examination of the blood showed a hemoglobin content of 11.22 Gm. per hundred cubic centimeters (66 per cent), with a red cell count of 3,210,000 and a white cell count of 2,500. The differential count showed 25 per cent polymorphonuclears, 23 per cent staff forms, 35 per cent lymphocytes, 10 per cent monocytes, 5 per cent atypical lymphocytes and 2 per cent eosinophils. The percentage of reticulocytes was 2.4. The Wassermann reaction of the blood was negative; urinalysis yielded normal results. The fragility of the red cells showed beginning hemolysis at 0.44 per cent and complete hemolysis at 0.30 per cent.

Initial roentgen studies showed a mass in the left upper quadrant of the abdomen, associated with distortion of the renal pelvis, with collapse of the major calices and inferior displacement of the kidney, which was interpreted as a possible neoplasm in the left kidney. Results of further roentgen examination after a barium sulfate enema and production of pneumoperitoneum were interpreted as giving evidence of a possible large retroperitoneal tumor mass, measuring about 8 by 15 by 19 cm., which was displacing the left kidney downward. After the oral administra-

tion of dye, roentgenograms of the gallbladder showed cholelithiasis. Studies of the long bones revealed nothing abnormal; hypertrophic changes were visible in the lumbar portion of the spine.

The anemia was refractory to all forms of treatment during the diagnostic study. On the twenty-sixth day of the patient's stay in the hospital an exploratory laparotomy was done by Dr. C. H. Waters with the patient under spinal anesthesia. The enlarged mass described was found to be due to a tremendously enlarged spleen, and splenectomy was performed. After removal the spleen weighed 2,060 Gm. The liver was slightly enlarged yet of normal appearance and consistency. A thick-walled gallbladder containing stones was encountered. The postoperative course was uneventful until the sixth day, at which time hypostatic pneumonia developed in the lower lobe of the left lung. At this time the blood count showed a hemoglobin content of 12.41 Gm. per hundred cubic centimeters (73 per cent), 4,970,000 erythrocytes and 11,200 leukocytes, with 45 per cent polymorphonuclears, 25 per cent staff forms, 21 per cent lymphocytes, 5 per cent monocytes, 2 per cent basophils and 2 per cent eosinophils. The congestion at the base of the left lung increased, and the patient became gradually weaker; he died on the thirteenth day after operation.

Pathologic Observations.—The spleen weighed 2,060 Gm. It was of essentially normal shape. The outer surface was rather deep in color, with numerous lymphoid follicles.

On section there are numerous lymphoid follicles, but relatively few show definite reaction centers. There are numerous small centers of fibrosis through the tissue, usually surrounded by zones of hypertrophied reticular cells with differentiation into free phagocytes. Sinusoids contain large numbers of these phagocytes, but they are usually not arranged in clumps. There is extensive red cell phagocytosis. Eosinophils are present in small numbers. There are scattered normoblasts but no definite erythropoietic foci.

No sternal aspirations were done on this patient.

Autopsy.—The site of the recent surgical operation was well healed. The heart was essentially normal. The left lung weighed 1,540 Gm., with almost complete uniform consolidation of the tissue, which on section proved to be typical lobar pneumonia. The splenic vein and artery each contained a thrombus extending through about the distal two thirds of the vessel. The thrombus did not extend into the portal vein or to the celiac axis. The liver was rather large and somewhat pale, with some degree of fatty degeneration evident in the section. The lymph nodes generally showed no abnormalities.

Case 5.—E. M., a white laborer aged 61, entered the University of Nebraska Hospital for the first time May 7, 1937, complaining of intermittent weakness since 1932. For several months during each of the past five years he had been forced to stop work because of fatigue. About eight months before admission to the hospital a diagnosis of pernicious anemia had been made elsewhere, and oral and intramuscular liver therapy had been instituted. Though considerable improvement was first noted, a severe relapse soon occurred while he was still under intensive liver therapy. Symptoms of marked weakness, dyspnea and palpitation on exertion, dizziness and a lemon yellow pallor had all been slowly progressive in spite of all types of antianemic therapy. He stated that he had had no symptoms of sore tongue, paresthesia or gastrointestinal disturbance. The past and family histories were noncontributory except that a brother had been jaundiced for a short time at the age of 20 years.

On physical examination the patient appeared well nourished. The temperature and the pulse and respiration rates were normal. There was a definite icteric tinge of the skin and scleras, and the mucous membranes were pale. The eyes, ears, nose and throat were normal except for the retinas, examined by Dr. Harold Gifford, which showed many scattered hemorrhages. There was no evidence of redness of the tongue or papillary atrophy. There were a few pea-sized cervical lymph nodes, but lymphadenopathy was not generalized. The lungs were clear, and the heart was not remarkable in rhythm or sounds. There was sclerosis (2 plus) of the radial vessels, and the blood pressure was 112 systolic and 72 diastolic. The spleen was enlarged, being palpable 7.5 cm. below the left costal margin, and was smooth and firm. There were no areas of abdominal tenderness, and no abnormal masses were palpable. The neurologic examination revealed nothing abnormal.

A blood count disclosed a hemoglobin content of 9.69 Gm. per hundred cubic centimeters (57 per cent), 2,860,000 erythrocytes and 3,200 leukocytes, with 30 per cent segmented polymorphonuclears, 31 per cent staff forms, 26 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. A smear of the red cells showed marked achromia with anisocytosis, poikilocytosis with a shift toward the macrocytic side, polychromatophilia and nucleated red cells (5 per hundred white cells). No spherocytes were noted. The mean corpuscular volume was 124 cubic microns; the mean corpuscular hemoglobin content, 32.4 micromicrograms, and the mean corpuscular hemoglobin concentration, 28 per cent. The percentage of reticulocytes varied from 10.3 to 14.3. The fragility of the red cells to hypotonic solutions of sodium chloride showed beginning hemolysis at 0.32 per cent. The platelets numbered 230,000. The bleeding and clotting times were normal with firm and rapid retraction of the clot. Urinalysis yielded normal results, and the Wassermann reaction of the blood was negative. Analysis of gastric contents showed 13 degrees of free acid and 27 degrees of total acid; examination of the stool did not reveal any blood. The basal metabolic rate was —8 per cent. The blood nonprotein nitrogen was 35 mg. per hundred cubic centimeters. The van den Bergh test showed a direct, delayed, slightly positive reaction, with a quantitative result of 17 mg. per liter. The bromsulphalein test for hepatic function showed 50 per cent retention after five minutes and 10 per cent after thirty minutes. A biopsy of bone marrow taken from the sternum revealed marked hyperplasia of the erythropoietic tissue.

Splenectomy was advised, but the patient refused, and he was dismissed from the hospital with instructions to take weekly intramuscular doses of liver extract and daily doses of reduced iron.

The patient returned to the hospital October 6 with a history of feeling moderately well until six weeks before admission, at which time he first noted vague pain in the upper part of the abdomen associated with frequent attacks of vomiting, increased pallor, deeper jaundice and progressive weakness. The stools were not clay colored, and the pain was not colicky at any time. He requested splenectomy at this time.

The results of physical examination were essentially the same as on the previous admission. The jaundice was definitely more marked and the spleen slightly larger, extending 8 cm. below the left costal margin.

The blood count revealed a hemoglobin content of 4.25 Gm. per hundred cubic centimeters (25 per cent), 1,000,000 erythrocytes and 1,400 leukocytes, with the same differential formula. The fragility of the red cells remained normal, but the percentage of reticulocytes had increased to 37.5, and the result of the quantita-

tive van den Bergh reaction was up to 68 mg. per liter. The icterus index was 35 units. The results of the remaining blood studies were essentially the same as those of the previous examination. Roentgenograms of the gallbladder failed to show any concentration of dye, and no opaque calculi were discerned. The roentgen study of the gastrointestinal tract showed no abnormality.

In an attempt to build up the patient's general physical condition before operation, intravenous injections of dextrose were administered frequently. In addition, transfusions of 500 cc. of whole blood, by the indirect citrate method, were given on two successive days. The hemoglobin content increased to 5.78 Gm. per hundred cubic centimeters (34 per cent), and the red cells to 1,250,000, with 2,600 white cells. Unavoidable circumstances prevented operation being performed at this time. The second day after the second transfusion the patient complained of a recurrence of the vague abdominal pain, which rapidly increased in severity. The jaundice became deeper; the spleen, tender to palpation. What first appeared to be an attack of biliary jaundice was really an acute hemolytic crisis, in which the blood count slowly decreased to 3.4 Gm. of hemoglobin per hundred cubic centimeters (20 per cent), 980,000 red cells and 2,250 white cells. The percentage of reticulocytes was 39; the icterus index increased to 50 units. The stool was highly colored at all times, and the van den Bergh reaction remained indirectly positive. Transfusions were resorted to again and two injections of 500 cc. each were given a day apart, with no apparent reaction. Though the general condition improved somewhat, the blood count decreased to 2.72 Gm. of hemoglobin per hundred cubic centimeters (16 per cent), 510,000 erythrocytes and 2,000 leukocytes, so that emergency splenectomy was performed October 27.

During the first forty-eight hours after operation, the patient's general condition was good and the jaundice noticeably lessened. He was given adequate fluid parenterally and a blood transfusion of 500 cc. immediately after operation and on each of the two succeeding days. On the third day after operation the hemoglobin content had increased to 6.97 Gm. per hundred cubic centimeters (41 per cent), the red cells to 2,210,000 and the white cells to 3,800. The jaundice had almost entirely disappeared. At this time the temperature was 103 F.; the pulse rate, 110 per miaute, and the respiratory rate, 35 per minute, associated with increasing abdominal distention. A large amount of serous fluid drained freely from the surgical wound, through which a small tag of omentum had appeared. Signs of free fluid in the abdomen became evident. The patient died the morning of the fifth day after operation, with increasing ascites and coma.

Pathologic Observations.—The spleen weighed 1,120 Gm. and measured 22 by 14 by 6 cm. The cut surface showed a rather brownish pulp with fairly distinct lymphoid follicles.

Sections show occasional lymphoid follicles with rather large reaction centers. The pulp is moderately congested. There are numerous eosinophils. There is moderate proliferation of reticular cells, which differentiate to form free phagocytes. These phagocytes occasionally appear in small collections in the sinusoids. Occasional ingestion of red blood cells is encountered. Normoblasts are frequent, and fairly numerous erythropoietic centers are seen.

Autopsy.—External examination revealed nothing unusual except the recent surgical incision in the left upper quadrant of the abdomen. Fifty to 100 cc. of fluid was encountered in the peritoneal and pleural cavities. The heart was entirely normal. The right lung showed a few small scattered areas of bronchopneumonic consolidation. The splenic vein was filled with a loosely adherent soft thrombus extending from the operative site to the portal vein and deeply into the liver.

No portion of this thrombus gave the impression of organization. Sections show that it is laminated and of a loose fibrinous character without organization. The gallbladder and the common bile ducts contained numerous small concretions, with no obstruction to the lumen. Sections of lymph nodes in various areas show no abnormalities.

The sternal marrow removed at autopsy shows approximately 50 per cent normoblasts, with no abnormal cells.

COMMENT

Etiology and Classification.—In attempting properly to evaluate this particular type of anemia, we must admit from the beginning that we have been completely puzzled as to the exact cause and the possible classification. Of the 2 males and 3 females in this series, all were adults whose ages varied from 25 to 62 years. The ages in 4 of the 5 cases ranged from 58 to 62 years. We, as well as others,[2] failed to elicit any history of previous similar attacks in childhood even after the most careful and repeated questioning. Investigation of some of the available relatives did not show evidence of an altered blood picture. The study of each individual case failed to reveal the fundamental cause of the hemolytic mechanism that obviously occurred in each instance. The signs of compensatory hyperactivity of the bone marrow were also a prominent feature. Beyond these facts, however, there was no further clinical evidence of the true basic cause of the disease process. Furthermore, postmortem examination in 3 cases gave no positive tangible clues as to the cause except possibly for the peculiar histiocytic reaction which occurred within the spleen. There was no evidence of the presence of accessory spleens or hemolymph nodes to account for the hemolytic process.

The refractory hemolytic anemia of which we are reporting cases should not be confused with congenital hemolytic jaundice, and the two disorders should be distinguished one from the other. In this respect, difficulty was encountered in attempting to gain help from the literature because of the diverse and often misleading terminology used by different authors. For example, some American writers frequently referred to this type of anemia as the acquired, or adult, type (Hayem-Widal) of hemolytic jaundice[3] or atypical hemolytic anemia.[4] Other authors[5]

2. (*a*) Davidson, N. S. P.: Macrocytic Hæmolytic Anæmias, Quart. J. Med. **1**:543-579 (Oct.) 1932. (*b*) Lovibond, J. L.: Macrocytic Hæmolytic Anæmia, Lancet **2**:1395-1399 (Dec. 21) 1935.

3. (*a*) Tileston, W.: Hemolytic Jaundice, Medicine **1**:355-388 (Aug.) 1922. (*b*) Rastetter, J. W., and Murphy, F. D.: Acquired Hemolytic Jaundice, Am. J. Digest. Dis. & Nutrition **4**:805-810 (Feb.) 1938.

4. Thompson, W. P.: Hemolytic Jaundice: Diagnosis, Behavior and Treatment, J. A. M. A. **107**:1776-1781 (Nov. 28) 1936.

5. Cheney, W. C., and Cheney, G.: Chronic Hereditary Hemolytic Jaundice, Am. J. M. Sc. **187**:191-212 (Feb.) 1934.

maintained that the acquired and the congenital form of hemolytic jaundice are essentially the same, that they differ only in the age period at which the clinical manifestations become apparent and that the fundamental defect is congenital. It is our opinion that many instances of the so-called acquired type of hemolytic jaundice are in reality congenital, because after a diligent and careful examination of other apparently "well" members of the families of several patients with such disease one of us (J. C. S.) has disclosed a number with a subclinical form of the disorder.[6] Some English authorities deny the existence of the acquired form of hemolytic jaundice,[7] while others designate such disease as macrocytic hemolytic anemia[8] or hemolytic (spherocytic) jaundice in the adult.[6]

Classification of the various hemolytic anemias has been vague and ill defined, chiefly because of the lack of sufficient information. The term hemolytic anemia has proved a useful dumping ground for many obscure diseases of the blood. There has been no clear and accepted definition of what constitutes hemolytic anemia. Pepper[9] has recently called attention to this discouraging state of affairs by asserting, "There are still large gaps in our knowledge of the fundamental process of erythrocytic destruction." He also emphasized the lack of clear separation between the various groups of so-called hemolytic anemias.

Hemolytic anemia appears in many guises and cannot be readily classified as a separate entity. No attempt will be made to classify this group of anemias in this report. In fact, we are not concerned with the hemolytic anemias associated with or secondary to such pathologic conditions as hepatic disease, Hodgkin's disease or leukemia[10] or with those due to sulfanilamide,[11] lead or infections of various types.[12] While in several of the cases reported by Thompson[4] so-called atypical

6. Sharpe, J. C.: Hemolytic Jaundice, Internat. Clin. **2**:146-147 (June) 1937.

7. (*a*) Dawson, B. E.: Hume Lectures on Hæmolytic Icterus, Brit. M. J. **1**:921-928 (May 30); 963-966 (June 6) 1931; (*b*) Indications for and Results of Removal of the Spleen, ibid. **2**:699-700 (Oct. 15) 1932. (*c*) Vaughn, J.: The Anemias, ed. 3, New York, Oxford University Press, 1936, pp. 229-251.

8. (*a*) Dyke, S. C., and Young, F.: Macrocytic Hæmolytic Anæmia Associated with Increased Red Cell Fragility, Lancet **2**:817-821 (Oct. 8) 1938. (*b*) Kremer, M., and Mason, W. H.: Acholuric Jaundices in the Adult, ibid. **2**:849-852 (Oct. 10) 1936. (*c*) Footnote 2.

9. Pepper, O. H. P.: A Survey of the So-Called Hemolytic Anemias, Ann. Int. Med. **12**:796-810 (Dec.) 1938.

10. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia, Ann. Int. Med. **12**:1782-1797 (May) 1939.

11. Kohn, S. E.: Acute Hemolytic Anemia During Treatment with Sulfanilamide, J. A. M. A. **109**:1005 (Sept. 25) 1937.

12. Parsons, L. G.: The Hæmolytic Anæmias of Childhood, Lancet **2**:1395-1401 (Dec. 17) 1938.

hemolytic anemia was secondary to reticulum cell sarcoma of the spleen, to syphilis or to tuberculosis, there were 9 cases in which no etiologic basis for the hemolytic anemia could be found. Israels and Wilkinson [13] raised the question of whether the cases they reported were instances of true hemolytic jaundice with unusual hyperplastic reaction within the spleen or primary disease of the spleen which had given rise to hemolytic anemia with acholuric jaundice. They expressed the opinion that the evidence supported the former view.

Dameshek and Schwartz [14] recently brought the whole question of the hemolytic syndromes into clearer focus by their experimental and clinical demonstrations of active serum isohemolysin. They expressed the opinion that the various blood pictures of the hemolytic anemias, viz., anemia, spherocytosis, increased fragility and reticulocytosis, are in all probability due to the effects of the varying amount and activity of hemolysins and are modified by the patient's power to react. Their work may well explain the common factor in such supposedly completely unrelated hemolytic syndromes as erythroblastosis foetalis, acute hemolytic anemia of Lederer, acute paroxysmal hemoglobinuria, "pernicious anemia" of pregnancy and up to and including acute or chronic hemolytic (spherocytic) anemia of either the congenital or the acquired type. Such interesting speculation is being further worked out by these authors. Unfortunately, no data were obtained in our studies which either confirm or oppose these views. Josephs,[15] on the contrary, expressed the belief that hemolytic anemia may be due to lack of some substance normally present in plasma, because he has isolated from human and from pig blood plasma a substance which reduces, if it does not completely inhibit, abnormal hemolysis in certain hemolytic anemias.

Davidson and Fullerton,[16] in a study of several cases of such anemia, were unable to offer any explanation for the blood destruction. They also expressed doubt that acute hemolytic anemia of Lederer could be separated from other hemolytic anemias merely because of the claim that blood transfusion apparently produced a cure. Along the same line of

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13. Israels, M. C. G., and Wilkinson, J. F.: Hæmolytic (Splenocytic) Jaundice in the Adult, Quart. J. Med. **7**:137-151 (Jan.) 1938.

14. Dameshek, W., and Schwartz, S. O.: The Presence of Hemolysins in Acquired Hemolytic Anemia: A Preliminary Note, New England J. Med. **218**: 75-80 (Jan. 13) 1938; Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemia with Particular Reference to the Nature of Spherocytosis and Increased Fragility, Am. J. M. Sc. **196**:769-791 (Dec.) 1938.

15 Josephs, H. W.: Studies in Hemolytic Anemia, Bull. Johns Hopkins Hosp. **62**:25-76 (Jan.) 1938.

16. Davidson, L. S. P., and Fullerton, H. W.: Some Rare Types of Macrocytic Anæmia, Quart. J. Med. **7**:43-85 (Jan.) 1038.

thought, Scott, Robb-Smith and Scowen [17] suggested the possibility that some obscure hemolytic anemias may be formes frustes of the Marchiafava-Micheli syndrome in which the hemolytic anemia is not sufficiently intense to produce hemoglobinuria. Dacie, Israels and Wilkinson [18] have demonstrated autohemolysis in vitro, which was shown to be dependent on the p_H of the system.

In summary, one can only say that it is impossible to make a coherent story out of the true etiology of hemolytic anemia at present. It remains obscure and in a state of confusion. However, with an increased number of cases of this disease being recognized and studied, an open mind should be maintained with an optimistic attitude toward the solving of the etiologic problems.

Clinical Manifestations.—The average duration of symptoms in this group of 5 cases varied from three months to five years. During the course of the disease the clinical picture varied considerably, from chronic (case 3) to subacute (cases 1, 2 and 4). In addition, the alternating periods of remission and relapse were well exemplified in case 5, in which they extended over five years. In no instance, however, was there any indication of a complete and spontaneous disappearance of symptoms after the disease process once became evident.

The clinical symptoms in these cases were those found in any hemolytic type of anemia, that is, weakness, pallor and jaundice. The onset was usually insidious. Loss of weight and a low grade fever were constant features in each case. Vague gastrointestinal disturbances, such as anorexia, epigastric distress, nausea and vomiting, and intermittent diarrhea were frequently present. Dizziness associated with palpitation and dyspnea on exertion was usually a less common complaint. Only 1 patient (case 1) had noted mild paresthesias of the extremities, whereas glossitis was significantly absent in all cases.

On examination all the patients presented various degrees of pallor, icterus and undernutrition. In 3 cases the patients were in a severely critical condition on admission to the hospital. During the observation period, a low grade fever was usually present, with the temperature ranging from 99 to 101 F. For the most part the jaundice was moderately severe, although the intensity would vary from time to time. Because of the hemolytic rather than obstructive character of the icterus, itching of the skin and bradycardia were absent. Splenomegaly was present in each instance. In cases 2 and 4 local pressure symptoms from

17. Scott, R. B.; Robb-Smith, A. H. T., and Scowen, E. F.: The Marchiafava-Micheli Syndrome of Nocturnal Hæmoglobinuria with Hæmolytic Anæmia, Quart. J. Med. **7**:95-115 (Jan.) 1938.

18. Dacie, J. V.; Israels, M. C. G., and Wilkinson, J. F.: Paroxysmal Nocturnal Hæmoglobinuria of the Marchiafava Type, Lancet **1**:479-482 (Feb. 26) 1938.

the enlarged spleen were encountered to such a degree that the possibility of a retroperitoneal or a pararenal tumor mass had to be excluded by roentgen examination of the genitourinary and the gastrointestinal tract before and after the production of a pneumoperitoneum. The liver was clinically interpreted as slightly enlarged in 2 cases, but without frank evidence of hepatic insufficiency or obstruction. In the 2 patients in whom the number of platelets in the blood was reduced (cases 2 and 3), a few mild purpuric spots were found in the skin.

As observed in persons with familial hemolytic jaundice, patients with this type of anemia were also subject to crises of acute blood destruction. During such an episode there was an acute exacerbation of all symptoms and signs, with increased jaundice, pallor, fever and splenomegaly. Epigastric distress occasionally became acute and colicky in nature. The hemoglobin content and the number of red cells decreased rapidly within twenty-four to forty-eight hours. In many instances no direct cause could be elicited for the initiation of these acute attacks. In cases 3 and 5, however, the crises immediately followed the transfusion of whole blood. These unexplained reactions following transfusion have been previously reported more fully, with a note of warning in the consideration of treatment.[19]

Laboratory Studies.—The blood in these cases showed a number of interesting and rather characteristic changes. The blood picture varied according to the balance between the mechanism of blood destruction and of compensatory blood formation. The degree of anemia was severe and profound in cases 1, 3 and 5, with the level of erythrocytes just at or under 1,000,000 cells per cubic millimeter. Initial erythrocyte counts in each of the other 2 cases were 3,200,000 and 4,650,000 per cubic millimeter. The erythrocytes were of the macrocytic type in 3 cases, the mean corpuscular volume averaging for the group 118 cubic microns; the mean corpuscular hemoglobin contents 37 micromicrograms, and the mean corpuscular hemoglobin concentration, 31 per cent. These observations are in agreement with those of Kremer and Mason (3 cases) [8b] and Dyke and Young (6 cases).[8a] The hematocrit reading in case 2 showed a hypochromic microcytic type of red cell. The data in case 4 were incomplete in this regard. In all but case 2 reticulocytosis was a striking feature, with the percentage of reticulocytes ranging from 8.4 to 71.6 and averaging 39.2 for the group. In case 2 on repeated examinations before splenectomy the patient had only 0.2 to 1.7 per cent reticulocytes. Studies of the stained blood smear for the presence of spherocytes, so characteristic of familial hemolytic jaundice, failed to reveal their presence in any case. Watson [10] has recently encountered

19. Sharpe, J. C., and Davis, H. H.: Severe Reactions Following Transfusion in Hemolytic Jaundice, J. A. M. A. **110**:2053-2056 (June 18) 1938.

increased fragility of the red cells in 2 patients with hepatic disease who had macrocytosis and increased blood destruction. In our cases, however, a number of fragility tests were carried out at different times, without definite or significant abnormality in the results. The tests were carried out before and after splenectomy and on various members of the patients' families who were available. The bleeding and clotting times, as well as the platelet count, showed little change in 3 cases but were somewhat decreased in cases 2 and 3.

Further preoperative hematologic investigation showed in each instance definite and persistent leukopenia, with the white cell count ranging from 1,400 to 4,000 per cubic millimeter. With the exception of case 1, in which there was some slight deviation toward the lymphocytic series, the differential formula was of normal distribution.

The degree of bilirubin present in the serum of these patients was measured by the icterus index, which ranged from 16 to 55 units, with an average of 34.4 units for the group. This hyperbilirubinemia varied from time to time in each case without apparent direct relation either to the degree of anemia or to the size of the spleen. The van den Bergh reaction was positive, usually being of the indirect type. The stools were highly colored with bile, and the reaction for urobilinogen in the urine was positive in dilutions of 1:40 to 1:200 in the 3 cases in which a test was made. Bilirubinemia as a result of obstructive jaundice was not encountered. Tests for hepatic function were performed in 2 cases, with normal results. Fractional analyses of gastric contents gave normal results except for achlorhydria in case 3. In the consideration of the differential diagnosis, the presence of free acid in the gastric contents should help rule out the possibility of pernicious anemia.

In all 5 cases cholecystograms disclosed the presence of biliary calculi. However, as far as we could determine, the cholelithiasis was not the cause of any episodes of colicky pain, obstructive jaundice or clay-colored stools before splenectomy. In case 2 the patient returned to the hospital one year after splenectomy with complaints typical of biliary colic. Subsequent examination of the calculi in 4 cases showed them to be composed chiefly of pigment and calcium salts. Apparently the mechanism for the production of biliary calculi which was present in these cases was similar to that frequently seen in cases of familial hemolytic jaundice.[20] Except for pressure defects from the enlarged spleen, roentgen studies of the gastrointestinal tract showed no gross abnormality which could account for the pathologic process.

Pathologic Observations.—There are several features common to the spleens in these 5 cases, as well as some differences. Grossly, all of the

20. Sharpe, J. C.: Hemolytic Jaundice: Clinical Analysis of Twenty-Eight Cases, Ann. Int. Med. **14**:953-959 (Dec.) 1940.

spleens were moderately to markedly enlarged, varying from 550 to 2,000 Gm. in weight. All were of essentially normal shape, that is, showing a general and uniform enlargement. Microscopically, all show reticulum cell hyperplasia as a striking feature, and in some this is the most prominent change. Reticulum cell hyperplasia can be traced through a series of differentiating cells to the formation of free phagocytes. These phagocytes appear in the sinuses in groups or clusters in several of the spleens, although the clumping is not present in all of them. These cells are characterized by rather large vesicular nuclei with prominent sharp chromatin strands and fairly deeply staining cytoplasm. Pigment in moderate amounts has been ingested, and in 4 of the 5 spleens these phagocytes have ingested erythrocytes in greater or smaller numbers. Marked phagocytosis of erythrocytes is evident in only 1 spleen. Normoblasts are present in all of the spleens. In some instances these are present in rather small numbers, while in others they are more numerous and definite erythropoietic foci can be made out. No megaloblastic differentiation is encoun red.

Polymorphonuclear and eosinophilic infiltration is present in all of the spleens in varying amounts, and eosinophils in particular are prominent in 3 of the 5 spleens. In only 1 is there evidence of granulopoiesis.

Only in case 3 is there a marked congestion of the pulp suggestive of the change characteristically seen in congenital hemolytic icterus. Three of the 5 spleens show lymphoid follicles rather widely scattered with little evidence of germinal centers. The other two spleens (cases 2 and 5) show well formed reaction centers.

The bone marrow studied was characterized by the marked predominance of erythropoietic activity. This is striking in view of the persistent anemia in this group of cases.

In the 3 cases in which postmortem examinations were done, particular attention was paid to the reticuloendothelial system of various organs and to the character of the lymph nodes. No abnormalities were noted in either tissue.

Differential Diagnosis.—The proper evaluation of these cases taxed the diagnostic acumen of the keenest clinician. It was necessary to obtain a detailed history and examination not only of the patient but of all the available relatives. Many various and repeated hematologic determinations were performed to help rule out other dyscrasias of the blood. Biopsy of sternal marrow for the study of bone marrow was necessary. After a careful and detailed period of study and observation, the clinicohematologic syndrome was tentatively placed in the unsatisfactory category of "hemolytic anemia." This was further substantiated

when it became evident that the anemia was apparently refractory to the usual forms of treatment. In the differential diagnosis, one must, of course, consider the following diseases of the blood:

Familial Hemolytic Jaundice: Though there is a superficial resemblance between familial hemolytic jaundice and the type of macrocytic hemolytic anemia reported here, there are a number of clinical differences, several definite hematologic dissimilarities and a striking and important difference in the result of treatment. Both diseases have in common the history of weakness accompanied by anemia, jaundice and enlargement of the spleen. Likewise, both syndromes are frequently complicated by secondary cholelithiasis. However, the macrocytic hemolytic anemias tend to occur in an older age group of patients who have not shown any previous clinical manifestations. In addition, there is no sign of the disease in other members of the family. In macrocytic hemolytic anemia the clinical course is usually more severe and of shorter duration than in familial hemolytic jaundice. Furthermore, the jaundice is more intense, the splenomegaly more marked and the hemoclastic crisis of blood destruction more protracted and serious in nature. In a study of the blood the anemia of hemolysis with hyperbilirubinemia and sustained, though varying, reticulocytosis is obvious in both conditions. However, instead of the microspherocytic type of red cell and the increased fragility, so characteristic of hemolytic jaundice, the erythrocytes of this type of hemolytic anemia are definitely macrocytic, with normal or only slightly altered fragility. In contradistinction to the normal leukocyte count or moderate leukocytosis of familial hemolytic jaundice, this group of macrocytic hemolytic anemias presents striking leukopenia. Finally, whereas splenectomy in familial hemolytic jaundice is the treatment of choice, with unquestioned excellent results, removal of the spleen in macrocytic hemolytic anemia is followed by little or only slight improvement in the hemolytic process. This striking difference in treatment between the two disorders will receive more emphasis later. Though one would consider such a differentiation relatively simple, the distinction between these two diseases may give rise to considerable controversy from the standpoint both of diagnosis and of treatment.

Acute Hemolytic Anemia of Lederer: This rather rare and acute hemolytic syndrome of unknown origin is usually most common in infants and young adults, rather than in persons of an older age group, such as those in the cases we are reporting. In addition, leukocytosis with myeloid immaturity and mild thrombopenia are rather important differences. Furthermore, a favorable reaction to blood transfusion, causing a dramatic and complete recovery, is a most helpful diagnostic, as well as therapeutic, point.

Banti's Disease: This chronic disease, often called splenic anemia, is a syndrome of splenomegaly, progressive anemia and leukopenia associated with a tendency to gastric hemorrhages, hepatic cirrhosis and ascites. Undoubtedly, there is more than one factor responsible for the clinicohematologic changes in Banti's disease. One realizes the anemia under discussion could not be included in this vague category when due consideration is given to the pathologic observations. The absence of fibrosis, the dilatation of the splenic sinuses, the esophageal varices and the changes in the hepatic tissues are striking differences in the two conditions. Furthermore, the anemia of Banti's disease is not hemolytic, and the bone marrow is usually normoblastic.[21]

Miscellaneous Diseases: Hodgkin's disease, pernicious anemia, aleukemic leukemia, reticuloendotheliosis, syphilis and malaria must be considered in the differential diagnosis, although distinctive characteristics of each disease make the separation relatively simple.

Treatment.—The importance of this group of grave anemias appears to be in the uncertainty of response to the various lines of treatment. In fact, in our cases the disease was characterized by a failure of all available antianemic remedies. It is our opinion that in the future when the basic underlying mechanism of the hemolytic process causing this disease is discovered and, if possible, removed or corrected, the anemia will show prompt improvement. This view is substantiated when we consider the presence of the hyperactive bone marrow and reticulocytosis, which are more than capable of restoring the circulating blood cells to normal, providing the destructive phase of the erythropoietic equilibrium is eliminated. Therefore, until this problem has been solved, one must be contented with a trial of the usual forms of treatment of any severe anemia, with the full realization of their shortcomings and the resulting grave prognosis.

Liver and Iron Therapies: We have been unable to see any beneficial effects from oral or parenteral iron or liver therapy, alone or in combination, with or without the vitamin B complex, either before or after splenectomy. This unsatisfactory response has also been the observation of others.[22] Intensive liver therapy has also failed to influence the existing degree of reticulocytosis. Though determinations of the amount of iron in the blood have not been performed in this group of cases, this perhaps should be done in the future. However, one would assume from the evidence at hand that no gross deficiency would be found.

Transfusion: Transfusion, as a temporary measure in acute episodes of destruction of the blood and as a routine preoperative procedure, has

21. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1939, pp. 283-284.

22. Dyke and Young.[8a] Kremer and Mason.[8b]

long been advocated by many authorities.[23] Certainly, transfusion is of distinct value in patients jaundiced as a result of biliary and hepatic disease.[24] However, the possible dangerous consequences of transfusions in cases of familial hemolytic jaundice were first pointed out by Lord Dawson [25] in 1931 and later by Hartfall and Stewart,[26] Doan and associates [27] and Lawrence.[28] After a careful analysis, they concluded it was impossible to determine definitely the underlying mechanisms of these transfusion reactions.

The same deleterious effect of transfusion has also been noted in these macrocytic hemolytic anemias. Cases 3 and 5 have served as a basis of a previous report.[19] In addition, Whitby and Britton,[21] as well as Kremer and Mason [5b] have warned of the possible harmful effects of transfusion during a crisis, and Payne [29] has recently reported a fatal reaction. It is our opinion that transfusion is also ineffective as a means of active treatment in the chronic form of this anemia. For example, in case 1 seven transfusions, totaling 3,240 cc. of whole blood, were given before splenectomy and four additional transfusions, amounting to 1,680 cc., after operation, without apparent effect. In other words, after 5 liters of blood was transfused over a period of eight weeks, the level of hemoglobin and red cells remained approximately the same. Lovibond [2b] and Israels and Wilkinson [13] have also had this experience. Since transfusion may at times cause the appearance of alarming symptoms, and even death in an already critically ill patient with macrocytic hemolytic anemia, and since the usual antianemic therapy with iron and/or liver extract is of little or no avail, it seems that one is left with but little to combat the acute episodes of blood destruction.

Splenectomy: Removal of the spleen was undertaken in all 5 cases only after the failure of the other forms of antianemic treatment became evident. One would naturally assume that in an anemia of unknown hemolytic character which had failed to respond to ordinary

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23. Hurxthal, L. M.: Hemolytic Jaundice: Consideration of the Diagnosis and Treatment, S. Clin. North America **15**:1475-1480 (Dec.) 1935. Tileston.[3a] Cheney and Cheney.[5]

24. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, J. A. M. A. **105**:1653-1658 (Nov. 23) 1935.

25. Dawson (footnote *7a* and *b*).

26. Hartfall, S. J., and Stewart, M. J.: Massive Paravertebral Heteropia of Bone Marrow in a Case of Acholuric Jaundice, J. Path. & Bact. **37**:455-459 (Nov.) 1933.

27. Doan, C. A.; Wiseman, B. K., and Erf, L. A.: Studies in Hemolytic Jaundice, Ohio State M. J. **30**:493-504 (Aug.) 1934.

28. Lawrence, J. S.: Indications for Splenectomy in Medical Practice, Internat. Clin. **2**:221-237 (June) 1937.

29. Payne, R. V.: Acute Hemolytic Anemia: Death After Transfusion, Guy's Hosp. Rep. **14**:65-71 (Jan.) 1934.

measures removal of a large portion of the destructive process (spleen) in the reticuloendothelial system would cause cessation or retardation of the anemia. In addition, a beneficial effect should be expected when the bone marrow is hyperplastic and there are a great number of young erythrocytes (reticulocytes) in the circulating blood stream attempting to compensate for the blood destruction. On this premise, splenectomy was performed in each of these 5 cases. However, the results were not those we expected. Special detailed blood studies were performed every few minutes during, and at longer intervals after, operation. In no instance was there the dramatic immediate change in the blood followed by a second more gradual and permanent effect, such as takes place in familial hemolytic jaundice. The details of these comparative studies are reported elsewhere.[1] In addition, these patients were poor operative risks and the postoperative complications much too frequent and severe. No such postoperative complications were observed in the 14 patients on whom splenectomy was performed of a group of 31 patients with familial hemolytic jaundice.[20] In our series of patients, 1 (case 5) died on the fifth day after operation of thrombosis of the splenic vein,[30] 1 (case 4) died of postoperative pneumonia one week after splenectomy and 1 (case 2) died of postoperative hemorrhage after a subsequent cholecystectomy, one year after splenectomy. Two patients (cases 3 and 1) are living five and a half and four years, respectively, after splenectomy with moderate, though certainly not complete, improvement. Both these patients continue to have a mild hemolytic type of anemia with leukocytosis but without the acute and severe clinical exacerbations and the crises of blood destruction observed before operation. In our experience we can only state that splenectomy has apparently helped to modify the hemolytic activity, but the clinical and hematologic results are still far from satisfactory.

That splenectomy does not favorably influence the course of macrocytic hemolytic anemia has been shown also by Scott and associates,[17] Lovibond [2b] and Whitby and Britton,[21] Kremer and Mason [6b] concluded that splenectomy is dangerous and unsuccessful in this type of anemia. In 2 of 4 cases reported by Thompson [4] the operation did not result in any change in the activity of the hemolytic process; in the other 2 cases the hemolytic process progressed, and the patients died. Davidson [2a] reported no benefit from splenectomy in 1 case; 1 other patient improved after operation, whereas a third patient improved without removal of the spleen. Israels and Wilkinson [13] reported 4 cases in which splenectomy caused a slow and incomplete recovery. Rastetter and Murphy [3b]

30. Davis, H. H., and Sharpe, J. C.: Splenic Vein Thrombosis Following Splenectomy, Surg., Gynec. & Obst. **67**:678-682 (Nov.) 1938.

removed the spleens of 2 patients; 1 of them improved, but the other had a relapse and died. Dyke and Young [8a] summarized their experience by stating:

> Splenectomy may slightly modify the course of the condition, but it does not cure and its results are in no way comparable to those of familial hemolytic jaundice. Its justification in this condition appears debatable.

SUMMARY

Clinical hematologic and pathologic observations in 5 cases of refractory hemolytic anemia in adults are presented.

The hemolytic phase of erythrocytic equilibrium with resultant macrocytic anemia failed to respond to the usual conservative methods of treatment.

In 2 cases transfusion produced dangerous and alarming reactions.

Splenectomy in each case failed to modify the course of the disease.

Postmortem observations in 3 cases are discussed.

ACUTE CORONARY THROMBOSIS IN INDUSTRY

I. DIRECT NONPENETRATING INJURIES, WITH REPORT OF CASES

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The occurrence of acute coronary thrombosis in workers during regular employment has added another facet to the many-sided picture of this clinical entity. The present broad and liberal compensation laws [1] definitely state that if a disease is caused, aggravated or precipitated by an incident arising out of and during the course of employment, then benefits should be paid and the employer assume the costs. A physician must determine whether the medical criteria of the law have been satisfied; namely, was a given incident capable of playing any etiologic role in the resulting disability? This should be a simple matter, but when the criteria are applied to acute coronary heart disease there is so much confusion and biased dogmatism that it is not unusual to find equally competent observers on opposite sides of the same question. This clinical study is presented in the hope of dispelling some of this confusion and of formulating a few broad principles which may aid in justly evaluating the compensability of any given injury, but with the realization that the future may change some of the present concepts.

MATERIAL

The patients in this study (except in case 5) were workers who sustained industrial accidents arising out of and during the course of employment, followed by acute cardiac conditions for which compensation benefits were claimed. The diagnosis, most often, was acute coronary thrombosis with myocardial infarction, but a better diagnostic term would have been acute traumatic heart disease with myocardial and pericardial damage. These clinical impressions rested on a varying combination of history, physical examination, first medical observations, electrocardiographic and roentgen studies and subsequent clinical course.

The injuries were divided into two large groups, namely, direct nonpenetrating (study I) and indirect injuries (study II) of the heart. The latter group included all those injuries or incidents which could in a remote manner influence the function and structure of the heart, for example, unusual effort, exposure to gases, increased atmospheric pressure or surgical shock.

1. Workmen's Compensation Law, New York, March 1, 1936, p. 6, paragraph 3, and p. 20, paragraph 2.

Direct nonpenetrating injuries result from an offending force applied directly to the chest without penetrating into its cavities, for instance, a blow; a kick; compression of the chest, or even of the abdomen [2]; impact of a steering wheel; striking the chest against a hard surface; jarring the contents of the chest, as in falling from a height, or perhaps the local application of massive doses of roentgen rays.[3]

Can a direct nonpenetrating chest injury damage the heart? The standard medical [4] and specialized cardiac [5] tests fail to answer this question, and a survey of the current literature revealed numerous reports without agreement on the part of various observers. A few citations will illustrate this diversity of opinion. Bright and Beck [6] collected a large series of cases of fatal heart damage following this type of injury, stressed the importance of early diagnosis and reported a number of cases of nonfatal damage. I [7] recently reported 9 cases of nonfatal injury of the heart, and Warburg's monograph [8] contained some valid examples of this type of heart damage. On the other hand, Stroud [9] commented editorially as follows: "This subject is most important from the standpoint of insurance compensation. I still feel cardiac disease is unusual following anterior

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2. Beck, C. S., and Bright, E. F.: Changes in the Heart and Pericardium Brought About by Compression of the Legs and Abdomen, J. Thoracic Surg. **2**:616, 1933.

3. Hartman, F. W.; Bollinger, A.; Doub, H. P., and Smith, F. J.: Heart Lesions Produced by Deep X-Ray: Experimental and Clinical Study, Tr. Am. Climat. & Clin. A. **43**:54, 1927. Thibaudeau, A. A., and Mattick, W. L.: Histological Findings in Hearts Which Have Been Exposed to Radiation in the Course of Treatment of Adjacent Organs, J. Cancer Research **13**:251, 1929. Werthemann, A.: Experimentelle Röntgenschädigungen des Herzmuskels, Strahlentherapie **38**:702, 1930.

4. Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1937. Osler, W.: Principles and Practice of Medicine, revised by T. McCrae, ed. 11, New York, D. Appleton and Company, 1930. Meakins, J. C.: The Practice of Medicine, St. Louis, C. V. Mosby Company, 1936. Emerson, C. P.: Textbook of Medicine, Philadelphia, J. B. Lippincott Company, 1936. Saville, A., and Warner, E. C.: System of Clinical Medicine, Baltimore, William Wood & Company, 1936. Yater, W. M.: Fundamentals of Internal Medicine, New York, D. Appleton-Century Company, Inc., 1938.

5. Levy, R. F.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936. Levine, S.: Clinical Heart Disease, Philadelphia, W. B. Saunders Company, 1937. White, P. D.: Heart Disease, New York, The Macmillan Company, 1932. Scherf, D., and Boyd, L. J.: Cardiovascular Diseases, St. Louis, C. V. Mosby Company, 1938.

6. Bright, E. F., and Beck, C. S.: Non-Penetrating Wounds of the Heart, Clinical and Experimental, Am. Heart J. **10**:293, 1935.

7. Leinoff, H. D.: Direct Non-Penetrating Injuries of the Heart, Ann. Int. Med. **14**:653, 1940.

8. Warburg, E.: Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-Penetrating Traumatic Injuries: A Clinical Study, New York, Oxford University Press, 1938.

9. Stroud, W. D., in Dick, G. F., and others: Year Book of General Medicine, Chicago, The Year Book Publishers, Inc., 1940, p. 699.

chest trauma." These opposing views indicate that physicians are divided over the possibility of heart disease being in any way caused, precipitated or aggravated by direct nonpenetrating injury of the chest.

As a basis for a critical study this material has certain inherent weaknesses, which should be mentioned. In no instance was it possible to duplicate at the bedside the ideal laboratory experiment of making observations before, during and after a given incident. On the contrary, it was necessary to reconstruct events weeks, months and even years later. A skilfully taken history and a thorough examination of all the previous medical reports and observations were important in bridging this gap of time and arriving at a fair clinical conclusion. It is realized that any attempt to relate a given incident to a subsequent pathologic condition is open to the criticism of "because of this, therefore that" type of thinking. This objection is not too valid, since present knowledge is incomplete and the physician's inability to explain a given event does not alter the fact of its occurrence. Besides, cause and effect were often too closely related to be merely coincidental.

REPORT OF CASES

CASE 1.—F. D., a 42 year old truck driver, stated that while he was unloading barrels of beer, one of the kegs rolled from the top, struck the front of the chest and threw him to the ground. On arising he was immediately aware of sharp, crushing cardiac pains and seemed unable to breathe. He finished the day's work in spite of symptoms, but about six hours later the pains became severe and crushing in nature, with rapid heart action, marked dyspnea, vomiting and profound weakness. A local physician made the diagnosis of acute coronary thrombosis with myocardial infarction. The past cardiac health had been good.

The patient was seen five days later, at which time he still complained of cardiac pains radiating to both shoulders, difficulty in breathing even while in bed, weakness, vomiting and rapid heart action after any exertion. The retinal arteries were moderately sclerotic. The heart was somewhat enlarged to the left; the sounds were of poor quality, were distant and lacked snap. The first apical sound was less intense than the second, and the second aortic sound was greater than the second pulmonic sound. Normal sinus rhythm was present, with a rate of 90 per minute. The blood pressure was 112 systolic and 80 diastolic. An obvious air hunger and mild shock were present. Serial electrocradiograms indicated acute myocardial damage in that part of the muscle supplied by a branch of the anterior coronary artery, or actually, sinus rhythm, left axis deviation and acute coronary thrombosis of the anterior type. The patient recovered, with marked curtailment of cardiac efficiency.

Comment.—Before the accident this man was in good clinical cardiac health, though he had some signs of sclerosis. He sustained a direct nonpenetrating injury of the chest, and immediately afterward symptoms developed, with a complete cardiovascular collapse within six hours.

CASE 2.—H. E., a 37 year old truck driver, stated that while he was removing a quarter of beef weighing about 150 pounds (68 Kg.) from a hook, it slipped out of his grip and struck the front of the chest rather forcibly. In a few moments he felt sharp pains around the heart but not enough to incapacitate him. These pains were continuous and were made worse by exertion, and within forty-eight

hours shortness of breath, weakness, dizziness and vomiting developed. A local physician made the diagnosis of acute coronary thrombosis. The past history was essentially normal, and hard physical work had been previously done without any difficulty.

This patient was seen nineteen days later, at which time the only complaints were occasional cardiac pains, weakness and excessive gas in the stomach. The heart was slightly enlarged to the left (roentgenogram taken at a distance of 6 feet [180 cm.]), the sounds were of poor quality, lacked snap and were distant. The first apical sound was less intense than the second, and the second pulmonic sound was equal to the second aortic sound, with a soft systolic murmur over the pulmonic valve. Normal sinus rhythm was associated with a rate of 80 per

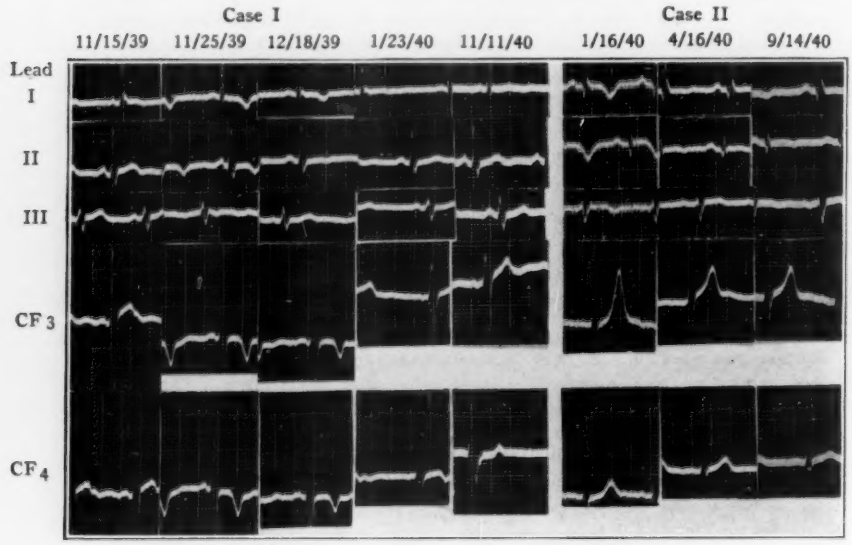

Fig. 1.—Electrocardiograms made in 2 cases of nonpenetrating injury of the chest.

minute. The blood pressure was 98 systolic and 65 diastolic. Serial electrocardiograms showed normal sinus rhythm, left axis deviation and changes indicating myocardial damage and acute coronary occlusion of the anterior type. A better interpretation would have been acute myocardial damage in that part of the heart supplied by a branch of the anterior coronary artery. The first few studies indicated the possibility of pericardial damage. Subsequent examinations indicated an enlargement of the heart, with marked limitation of cardiac function.

Comment.—This man was in good clinical health until he sustained a blow to the anterior portion of the chest. Symptoms immediately developed which culminated in a complete cardiac collapse within forty-eight

hours. The original electrocardiograms indicated the possibility of pericardial and myocardial damage.

CASE 3.—H. A., a 38 year old porter, stated that while he was unloading a hand truck, it started to move and threw him off balance; one of the bundles, weighing about 25 pounds (11 Kg.), became dislodged, fell and struck the front of the chest sharply. He felt as though his breath had been knocked out and in a few moments was aware of a burning sensation extending down from the neck to the pit of the stomach. He continued working, but the symptoms became so bad at the end of six hours that medical aid was sought, and a diagnosis of acute coronary occlusion was made. The past cardiac history was normal.

The patient was seen about three and one-half months later, complaining of occasional strange feelings around the heart and an inability to lie on the left side but without any serious curtailment of cardiac function. The eyegrounds showed minimal arteriosclerosis. The heart was slightly enlarged, with some dilatation of the first portion of the aorta; the sounds were of fair quality. The first apical sound was less intense than the second, and the second aortic sound was equal to the second pulmonic sound. Normal sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 135 systolic and 90 diastolic. The functional tests showed a good cardiac reserve. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, myocardial damage and coronary occlusion of the anterior type.

Comment.—This man was in good clinical health until he sustained a trauma to the anterior portion of the chest. Signs and symptoms immediately developed which led to complete collapse within six hours. There were some signs of sclerosis in the eyegrounds and in the aorta.

CASE 4.—J. R., a 45 year old truck driver, stated that in the process of unloading poultry he was struck over the front of the chest by a crate of chickens and immediately became unconscious. He was removed to Morrisania City Hospital, where he remained for a considerable period, complaining of precordial pains, exertional dyspnea and profound weakness. At this institution the diagnosis was acute coronary thrombosis of an unclassified type. The past history was normal.

This man was first seen four years later, in order to evaluate his cardiac status for an operation for hernia. He still complained of exertional dyspnea, inability to lie flat, rapid heart action and effort angina. The retinal arteries were sclerotic. The heart was slightly enlarged; the sounds were of fair quality, and sinus rhythm was present, with a rate of 85 per minute. There was a soft systolic blow at the apex; the first apical sound was louder than the second, and the second aortic sound was greater than the second pulmonic sound. The blood pressure was 120 systolic and 75 diastolic. Roentgen studies showed a moderate dilatation and elongation of the first part of the aorta, with a systolic bulge along the lower half of the left cardiac border. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, ventricular extrasystoles, myocardial damage and possible coronary closure of an unclassified type. There was moderate loss of cardiac efficiency.

Comment.—This patient was in good clinical health until he was struck in the chest. He immediately became unconscious, was hospitalized and after his recovery showed persistent signs of insufficiency of the coronary circulation.

Case 5.—J. M., a 48 year old practicing surgeon, was in an automobile accident, during which the front of the chest was forcibly jammed against the steering wheel. He was dazed, momentarily lost consciousness and then became aware of severe pain over the sternum, rapid heart action and an inability to catch his breath. The pains were made worse by moving, coughing or deep breathing. In addition, there were headaches, dizzy spells and a great deal of body ache. The past history was normal.

This patient was seen thirteen days later, complaining of weakness, cardiac pain, exertional dyspnea and rapid heart action. The left side of the chest was tender on pressure, but roentgen examination failed to show any fractures. The lungs were normal. The heart was normal in size; the sounds were of fair quality. The first apical sound was louder than the second, and the second aortic sound

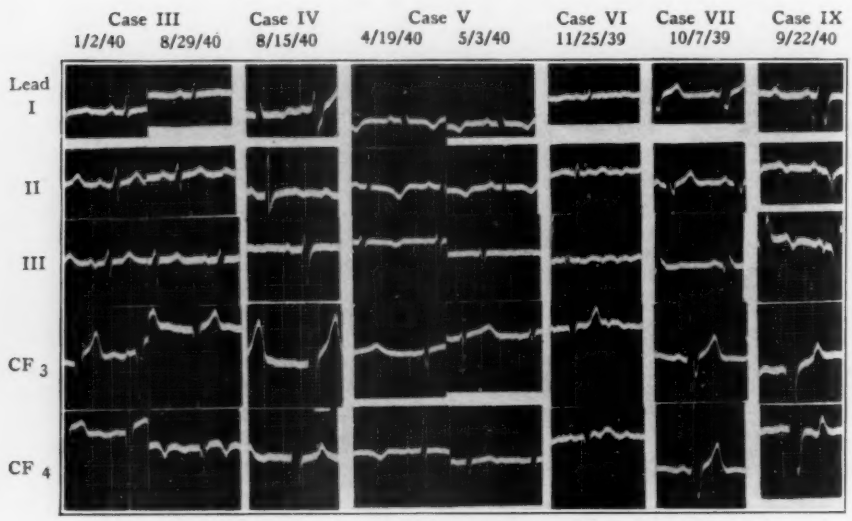

Fig. 2.—Electrocardiograms made in 6 cases of nonpenetrating injury of the chest.

was greater than the second pulmonic sound. The blood pressure was 138 systolic and 80 diastolic. Serial electrocardiograms showed progressive myocardial changes characteristic of anterior coronary closure, sinus rhythm and left axis deviation. The patient made an uneventful recovery and returned to work without any impairment of function.

Comment.—Though this case does not represent an industrial accident, it was included because of the nonpenetrating injury of the chest and the heart damage. Immediately after the accident cardiac signs and symptoms developed. The functional recovery was good.

Case 6.—G. E., a 43 year old janitor, lost his balance and fell down a flight of stairs, striking the head, chest and back. He was somewhat dazed and a few

minutes later became unconscious. He was admitted to the hospital with throbbing pains in the head, marked shortness of breath, rapid heart action and an inability to speak. These symptoms subsided and his ability to speak returned. After his discharge there were persistent shortness of breath, exertional rapid heart action and edema of the ankles, which became so bad that it was necessary for him to reenter the hospital. At this time the diagnosis was rheumatic mitral stenosis, auricular fibrillation and moderate cardiac decompensation. The past history indicated syphilitic infection and an attack of rheumatic fever with involvement of the heart in 1935. The past cardiac functional status was good.

This man was seen ten months after the injury, still complaining of exertional dyspnea, cardiac pains and some swelling of the ankles. The retinal arteries showed some arteriosclerosis. There was a moderate amount of congestion of the bases of both lungs. The heart was enlarged to the left and to the right, and on fluoroscopic examination there was a marked prominence of the right auricle, with a moderate enlargement of the rest of the heart. The heart sounds were of poor quality. Auricular fibrillation was present, with a ventricular rate of 95 per minute and a pulse deficit of 20. The first apical sound was replaced by a systolic murmur. A diastolic murmur was present along the left sternal margin. The second pulmonic sound was louder than the second aortic sound. The liver was enlarged 2 fingerbreadths below the costal margin, and there was pitting edema (1 plus) over both extremities. The blood pressure was 110 systolic and 80 diastolic. The electrocardiographic diagnosis was auricular fibrillation, with a controlled ventricular rate, changes suggestive of myocardial damage and residual signs of anterior coronary occlusion, as indicated by the absence of the R wave in lead IV. The patient remained under observation, and during the latter part of 1940 he had a cerebral accident and died.

The report of the postmortem examination was as follows: "The heart is enlarged both to the right and to the left. The right auricle is larger than normal. The tricuspid valve is normal. The left ventricle is enlarged, and the endocardium is grayish white and firm; it shows evidence of fibrosis; the pulmonic valve is normal. There is marked arteriosclerosis along the course of the pulmonary artery at its bifurcation. There is no evidence of pulmonary embolism. The mitral valve looks like a funnel and admits the tip of one finger only. There is a large, fresh, friable vegetation along the line of closure. The mitral valve is thickened and calcified in some areas. The chordae tendineae are thickened and shortened. The papillary muscles seem to be implanted on the valve. The large thrombus formation just noted is present in the dilated left auricle. An aneurysmal dilatation about the size of a quarter is present at the apex, with the myocardium markedly thinned out on the left side. White strands stand out prominently on the endocardial surface of the left ventricle. The aortic valve is normal in size; the cusps are thin and delicate, and the commissures are not widened. There are isolated arteriosclerotic plaques along the course of the aorta. The ostiums of the coronary arteries are patent. The coronary vessels are sclerotic and the lumens narrowed. There is no evidence of occlusion, however."

Comment.—According to his history, this patient was in good clinical health aside from a quiescent rheumatic infection of the mitral valve. He was able to do regular hard work without any difficulty. After the injury to the chest he became unconscious and from then on presented cardiac symptoms. In addition, there was a transient cerebral involve-

ment. The diagnosis was mitral stenosis, auricular fibrillation and possible traumatic injury to that part of the heart supplied by a branch of the anterior coronary artery. There were an underlying rheumatic infection, sclerosis of the coronary arteries and possibly syphilis, all confirmed at autopsy. The small aneurysmal dilatation of the left ventricle located near the apex, but not associated with any coronary closure, in retrospect may have been the site of a contusion and subsequent scarring. This is speculative, but if all the facts are kept in mind it does not seem an unreasonable possibility.

Case 7.—M. D., a 52 year old foreman of a milk-loading depot, lost his balance and fell, striking the front of the chest sharply against the conveyor and a case of milk. He immediately felt weak and dizzy and was conscious of rapid heart action. He rested a short while but noticed that any effort brought on symptoms which became so bad three days later that he applied for medical aid. Before the injury he was in good physical health and had been doing hard physical work on one job for twelve years without any loss of time.

This man was examined two and one-half months later, still complaining of exertional dyspnea, marked weakness and dizziness. He appeared much older than his stated age. The retinal arteries were moderately sclerotic. The heart was normal in size; the sounds were distant, muffled and of poor quality over the base. Normal sinus rhythm was present, with a rate of 80 per minute. The first apical sound was equal to the second, and the second pulmonic sound was greater than the second aortic sound. The blood pressure was 108 systolic and 88 diastolic, and after a functional test the pulse rate remained elevated. Roentgen examination revealed diminished movements of the left lower border of the heart. An electrocardiogram revealed a normal sinus rhythm, ventricular extrasystoles, right axis deviation, changes indicative of myocardial damage and possibly residual signs of an atypical coronary closure.

Comment.—This patient was in good clinical health until the chest was traumatized. Immediately, he displayed signs and symptoms of insufficiency of the coronary circulation which were progressive and became so bad in three days that work was discontinued. Serial electrocardiograms failed to reveal the progressive changes usually associated with fresh myocardial lesions. If the past history is true, then this injury immediately changed the clinical status of this man.

Case 8.—A. J., a 64 year old druggist, was struck by an automobile while he was crossing the street. He was admitted to the Flower and Fifth Avenue Hospitals in shock, unconscious and cyanotic, with a slow pulse. Roentgenograms showed fractures of the fourth, fifth, sixth, seventh and eighth ribs on the left side; multiple fractures of the pelvis, and a left hemothorax. He gradually recovered from the shock but continued to complain of severe pain in the chest and other parts of the body. Five days later, after a bowel movement, he suddenly became dyspneic and cyanotic and exhibited all the signs of shock and collapse. The past history was normal.

This man was seen seven days after the accident and presented essentially the same picture as just described. The heart was slightly enlarged, and the

sounds were of poor quality. The first apical sound was less intense than the second and the second pulmonic sound was greater than the second aortic sound. Normal sinus rhythm was present, with a rate of 65 per minute, and the blood pressure was 155 systolic and 55 diastolic. There was some fluid in the left pleural cavity. Serial electrocardiograms revealed changes suggestive of an acute type of heart damage. He made an uneventful recovery, but the fractures precluded any clinical evaluation of cardiac function.

Comment.—This patient was in good clinical health until he sustained a rather severe type of injury. It is interesting to note that on admission, in spite of the shock, the patient's pulse was rather slow. This phenomenon has been noted in some experimental animals.[10] The care of the fractures dominated the clinical picture, and it was not until the

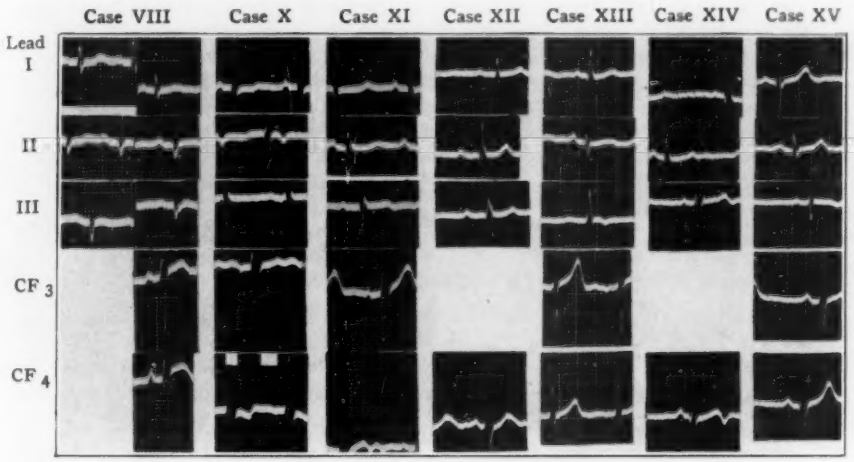

Fig. 3.—Electrocardiograms made in 7 cases of nonpenetrating injury of the chest.

patient had a complete cardiac collapse that investigation revealed signs of acute heart damage. This acute condition may have represented a pulmonary embolus or a spontaneous coronary occlusion, but subsequently the classic picture of either of these two conditions did not develop. The extensive type of chest injury suggested a traumatic factor in the cardiac picture.

Case 9.—P. K., a 62 year old porter, stated that while backing a load of wood, he lost his balance and fell, striking the left side of the chest sharply against the handle of the truck. In addition, he hurt his hip, leg and scrotum. He immediately felt sharp pains around the heart and was unable to breathe properly. He was given

10. Moritz, A. R., and Atkins, J. P.: Cardiac Contusions: An Experimental and Physiologic Study, Arch. Path. **25**:445 (April) 1938.

local treatment, but the symptoms, particularly the shortness of breath, became so bad that he was put to bed for six weeks. He then returned to do light work, but the dyspnea, precordial pains and weakness persisted. These symptoms were progressive, and the patient finally collapsed with severe cardiac pains, vomiting and shortness of breath about two months later. Since then he has remained at home and has been unable to work because of these symptoms. The roentgenogram showed a fracture of the ribs on the left side. In addition, there was a traumatic hydrocele of the right testicle. Before the accident he had been in good health and was able to do hard physical work, without any limitations.

This man was examined about three years after the original accident and still complained of exertional dyspnea, cardiac pains and swelling of the right testicle. The retinal arteries showed moderate arteriosclerosis. There was a hydrocele of the right testicle. The heart was enlarged, and the aorta was somewhat dilated. The heart sounds were of fair quality but lacked snap; the first apical sound was louder than the second, and the second aortic sound was greater than the second pulmonic sound. There was a short systolic murmur at the apex. The blood pressure was 122 systolic and 70 diastolic, and a few rales were present over the bases of both lungs. A simple bending exercise produced air hunger. The electrocardiogram revealed a normal sinus rhythm, left axis deviation, changes indicative of myocardial damage and possible residual signs of posterior coronary thrombosis. There was rather extensive limitation of cardiac efficiency.

Comment.—This patient was in good clinical health until he sustained a rather severe direct nonpenetrating injury of the chest. He immediately displayed signs and symptoms which persisted and finally culminated in complete cardiac collapse.

Case 10.—C. K., a 54 year old truck driver, stated that while he was waiting for a red traffic light to change, the rear of his truck was hit by another car, and his chest was violently thrown forward against the steering wheel. At the same moment his right foot, which was on the foot brake, was violently pushed upward and caused a compression of the leg on the abdomen. He was immediately aware of severe pains in the abdomen, heart and head. These symptoms and exertional dyspnea persisted and gradually became worse. Two weeks later, while carrying a heavy object up three flights of stairs, he suddenly collapsed with severe cardiac pain, nausea, vomiting, weakness and dyspnea. He was put to bed and presented the clinical picture of a complete cardiac breakdown, with edema of the ankles. The past history indicated no difficulty in doing hard work for the preceding twelve years.

This man was seen about a year and a half later, at which time he complained of precordial pain radiating to the shoulder, dyspnea, dizzy spells, weakness and a lump in the stomach. The eyegrounds showed arteriosclerosis (1 plus). The chest was barrel shaped. The heart was moderately enlarged. The aorta was somewhat dilated, and the left cardiac margin showed diminished movements. The heart sounds were of poor quality, were muffled and lacked snap. The first apical sound was less intense than the second, and the second aortic sound was equal to the second pulmonic sound. Normal sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 118 systolic and 90 diastolic. The liver was enlarged and tender. After a simple bending exercise the patient showed obvious air hunger. The electrocardiogram revealed a normal sinus rhythm, left

axis deviation, changes indicative of myocardial damage, coronary occlusion of the posterior type and changes due to digitalis therapy. There was marked curtailment of cardiac function.

Comment.—This patient was in good clinical health until he sustained a direct nonpenetrating injury of the chest. Immediately signs and symptoms developed which persisted and ended in the subsequent collapse.

CASE 11.—J. M. R., a 55 year old salesman, stated that the car he was driving skidded and struck an elevator pillar. His chest was forcibly crushed against the steering wheel. He was immediately aware of precordial pains, weakness and some difficulty in breathing. After being allowed out of bed he noticed excessive shortness of breath and exertional distress. Before the injury there had been similar symptoms but evidently not severe enough to interfere with his work.

This patient was seen about four months after the injury, with the same complaints. The eyegrounds showed some arteriosclerosis. The aorta was somewhat dilated and elongated. The heart was moderately enlarged to the left. The heart sounds were of poor quality and lacked the characteristic normal snap. The first apical sound was equal to the second, and the second pulmonic sound was equal to the second aortic sound. The blood pressure was 168 systolic and 104 diastolic. The electrocardiographic diagnosis was normal sinus rhythm, changes indicative of myocardial damage, left axis deviation and possible residual signs of posterior coronary occlusion.

Comment.—There was some disability before the accident due to the coronary sclerosis but not enough to keep the patient from working. After a direct nonpenetrating injury of the chest signs and symptoms developed which ultimately led to complete disability.

CASE 12.—L. K., a 60 year old plumber, fell from the top of a ladder and struck his chest rather sharply against the ground. He immediately felt weak, had a desire to vomit and experienced difficulty in breathing. He rested for a while and then attempted to work. In addition to the symptoms just mentioned, he noticed a pressing sensation in the pit of the stomach and under the breast bone. These symptoms continued, gradually becoming worse, and about a month later, while carrying his bag of tools, weighing 65 to 75 pounds (30 to 34 Kg.) up four flights of stairs, he collapsed with severe pains in the chest, weakness and dizziness. The past history was normal.

This man was first seen about six months after the accident, with essentially the same complaints. The heart was slightly enlarged; the heart sounds were of poor quality; the first apical sound was equal to the second, and the second aortic sound was equal to the second pulmonic sound. The blood pressure was 130 systolic and 85 diastolic. The electrocardiogram revealed normal sinus rhythm, first degree heart block and changes indicative of myocardial damage.

Comment.—This patient was in good clinical health until he sustained a direct nonpenetrating injury of the chest. Cardiac symptoms then developed which were progressive and culminated in complete collapse.

CASE 13.—A. K., a 46 year old manager of a bakery shop, slipped and fell down a flight of stairs, striking the lower portion of his chest and back on the left side. He immediately felt pain in the chest, rapid heart action, weakness and dizziness. These symptoms persisted, and a few hours later, the patient began to vomit and the pains returned in a severe form. A diagnosis of coronary occlusion was made. Before the accident the patient had been doing hard physical work without any difficulty.

This man was first seen four months later, complaining of exertional pain and dypsnea, rapid heart action and spells of dizziness and weakness. The eyegrounds showed moderate arteriosclerosis. The heart was moderately enlarged, and the sounds were of a fair quality. The first apical sound was equal to the second, and the second pulmonic sound was equal to the second aortic sound. There was a systolic murmur at the apex. The blood pressure was 152 systolic and 116 diastolic. The electrocardiogram showed normal sinus rhythm, left axis deviation, changes suggestive of myocardial damage and residual signs of coronary occlusion of the nonclassified type. There was moderate curtailment of cardiac efficiency.

Comment.—This patient was in good clinical health until he sustained a nonpenetrating injury of the chest. Immediately he exhibited signs and symptoms of acute insufficiency of the coronary artery circulation.

CASE 14.—A. K., a 65 year old janitress, tripped over a floor mop and fell, striking the head, face and front of the chest. She immediately felt sharp pain in the chest and seemed unable to breathe. Her subsequent complaints were exertional dyspnea and cardiac pains, weakness and edema of the ankles. Though she stated her past history was normal, testimony indicated she had preexistent angina pectoris; however, there was no doubt about the accident.

This woman was seen four months later with the same complaints. The eyegrounds were mildly sclerotic. The heart was enlarged. The heart sounds were of fair quality, though lacking in snap. The first apical sound was louder than the second, and the second aortic sound was equal to the second pulmonic sound. There was a soft systolic murmur at the apex. The blood pressure was 130 systolic and 70 diastolic. There was slight congestion at the bases of both lungs. After a simple bending exercise there was obvious air hunger. The electrocardiogram showed left axis deviation, normal sinus rhythm, changes indicative of myocardial damage and residual signs of posterior coronary occlusion.

Comment.—This case illustrates the importance of the past history. The patient evidently had antecedent angina pectoris with clinical symptoms. Without an accurate history the whole cardiac picture would have been attributed to the fall, whereas this injury only aggravated her previous condition.

CASE 15.—A. W., a 61 year old painter, fell from the top of a ladder, a distance of 6 feet (183 cm.) and struck the chest and body and fractured the right os calcis. He immediately felt pains in the foot and over the heart. While in bed, he complained of cardiac pains, dizzy spells and weakness. When he resumed his activities, he noted a persistent shortness of breath which had not been present

before. On returning from the first visit to his physician, it was necessary for him to climb four flights of stairs on crutches. This started a great deal of cardiac pain, dyspnea, dizziness and weakness, and a diagnosis of coronary occlusion was made. The past history indicated ability to do hard physical work without any difficulty.

This patient was first seen three months after the accident, with essentially the same complaints. The retinal arteries showed some sclerosis. The heart was slightly enlarged; the lower left margin showed decreased movements, and the aorta was somewhat dilated. The heart sounds were of poor quality; the first apical sound was louder than the second, and the second aortic sound was greater than the second pulmonic sound. Normal sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 112 systolic and 80 diastolic. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, myocardial damage and possible residual signs of posterior coronary occlusion. There was marked curtailment of cardiac efficiency.

Comment.—This patient was in good clinical health until he sustained a direct nonpenetrating injury of the chest. Cardiac symptoms then developed, and after the unusual exertion of climbing four flights of steps on crutches for the first time, he sustained an acute coronary occlusion. In this patient there is a combination of a direct and an indirect trauma. It is possible that the former produced little damage and that the latter was mainly responsible for the clinical picture which followed.

Case 16.—M. G., a 48 year old store clerk, stated that he slipped and fell on a flight of stairs, striking the front of the chest rather sharply. The injured part felt bruised, but no shortness of breath, weakness, etc., were noted at the time. He continued working for five hours without any difficulty. That same night he was awakened from a sound sleep (twelve to fourteen hours after the injury) by sharp, squeezing precordial pains. He was kept in bed the following day; the symptoms subsided, and he then returned to work. This time he engaged in his regular occupation for twelve hours without noticing any unusual symptoms, but that same night after having fallen asleep he was awakened by severe substernal pains, nausea, vomiting, weakness, rapid heart action and dyspnea. A diagnosis of acute coronary occlusion was made. He gave a past history which did not include any previous cardiac complaints and stated that he had been able to do hard work without any difficulty. However, his physician gave a history of a similar attack of angina, vomiting, weakness and change in blood pressure occurring about eight months before the present illness.

This patient was seen six days after the accident and complained of the same symptoms just noted. The eyegrounds were sclerotic. The heart was boot shaped and moderately enlarged to the left; the aorta was dilated and elongated. Normal sinus rhythm was present, with a rate of 75 per minute. The sounds were of poor quality and muffled; the first apical sound was less intense than the second, and the second pulmonic sound was greater than the second aortic sound. The blood pressure was 120 systolic and 80 diastolic (at the time of the first attack it had been 230 systolic and 120 diastolic). During this examination, rather strong pressure over the precordium with the stethoscope failed to elicit any complaints

of pain and no external signs of injury were present. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, myocardial damage and acute coronary thrombosis of a posterior type.

Comment.—This case was particularly instructive. If the physician's account of the patient's history is accepted, during the first night after injury the patient had a severe attack of angina, from which he recovered, and two nights later a coronary occlusion developed, both on the basis of hypertensive arteriosclerotic heart disease. With this history in mind one may doubt that the patient even had a fall, inasmuch as this was not reported to any one at the time of its occurrence and may have been a thought in retrospect.

On the other hand, if the patient's history is accepted, it will be noted that no cardiac symptoms appeared until many hours after the injury. The complete breakdown occurred forty-eight hours later while the patient was asleep and after he had worked twelve hours without any difficulty. In the experimental reports signs and symptoms appeared and persisted after the trauma. In the presence of a hemopericardium it is possible that some symptoms would appear, but the total breakdown would be delayed. A contusion of the myocardium would produce functional disturbances at once and not after a delay of forty-eight hours or longer. In this case the injury, if it did occur, was only incidental.

Case 17.—R. F., a 49 year old laborer, fell from an 8 foot (244 cm.) ladder, striking his head, the lower part of the back and the chest. One of the lumbar vertebrae was fractured, and a cast was applied. At this time and subsequently he complained of local pains. Eight months later he suddenly fainted and remained unconscious for five hours. Since then there have been shortness of breath, swelling of the ankles, rapid heart action, precordial pain and weakness. The past history was essentially normal.

This man was seen about nine months after the accident, complaining of the symptoms just mentioned. The heart was enlarged. The sounds were of poor quality and seemed somewhat distant. Auricular fibrillation was present but without any murmurs. The ventricular rate was 90 per minute, with a pulse deficit of 30. The blood pressure was 110 systolic and 80 diastolic. The electrocardiographic diagnosis was auricular fibrillation, myocardial damage and changes due to digitalis therapy, with a slow ventricular rate.

Comment.—This case was included because a claim was made for the cardiac disability on a traumatic basis. The patient evidently suffered an acute coronary occlusion about eight months after the accident. In view of clinical and experimental experience this could in no way have been related to the original injury because of the time interval. Here again an accurate history was important.

Case 18.—S. B., a 33 year old florist, slipped on a wet floor and fell, striking the front of the chest sharply against the edge of an ice box. He was immediately

aware of sharp cardiac pains, difficulty in breathing and extreme weakness. The left leg was bruised against a pail on the floor. Within six hours the thoracic pains became so bad that he was put to bed by his physician. At this time there were signs of external injuries, such as discolorations and small abrasions. After several weeks the symptoms subsided. The past history was normal.

He was seen three weeks later, complaining of slight cardiac pains. The heart was normal in size, position and movements. The heart sounds were of good quality; the blood pressure was 110 systolic and 70 diastolic, and the lower end of the sternum was tender on pressure. The electrocardiographic diagnosis was

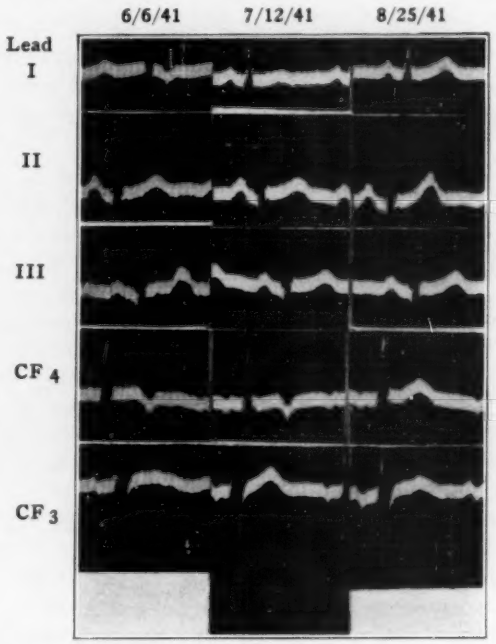

Fig. 4.—Electrocardiograms made in a case of nonpenetrating injury of the chest.

normal sinus rhythm, absence of axis deviation and acute myocardial damage in an area supplied by the anterior coronary artery. This was confirmed by serial tracings.

Comment.—This man exhibited acute electrocardiographic changes after a chest injury. This case illustrates the importance of electrocardiographic study in all instances of trauma to the chest. The functional recovery was complete several months later. This case is not included in the section headed "Comment."

COMMENT

Incidence.—No accurate statistics are available as to the frequency of nonfatal cardiac damage after nonpenetrating injuries of the chest. The numerous current reports indicate that this is not a clinical rarity and that the condition will probably be recognized more often in the future.

Sex.—All except 1 of the patients were males. This predominance is probably due to the more strenuous physical tasks performed by men in industry.

Age.—Only 2 patients were under 40 years of age, and the rest were evenly distributed among the fourth, the fifth and the sixth decade. Young and old persons alike are subject to this type of injury, but in the latter an underlying quiescent process may complicate the resulting picture.

Occupation.—The actual nature of the work was not as important as the kind of accident. In the whole group of cases the injuries were evenly divided between the light and the heavy industries.

Trauma.—The injury was considered an important etiologic factor in the first 15 cases and only as incidental in the last 2 (cases 16 and 17). The offending force varied as to quality, quantity and point of application.

The chest was injured by heavy objects in 34 per cent of cases (1, 2, 3, 4 and 9); by striking a hard surface, as in falling, in 40 per cent of cases (6, 7, 12, 13, 14 and 15), and by automobile accidents in the remaining 26 per cent of cases (5, 8, 10 and 11). In this last group, the injury was caused by impact with a steering wheel in 3 cases and in 1 case the patient was struck by a car.

The anterior part of the thorax on the left side was the point of application in 10 cases and the left side and the back of the thorax in 5 cases. These figures are the same as those in current reports in the literature.

A rough division indicated that the offending force was moderate in 9 cases, rather severe in 5 cases and mild in 1 case.

External signs of injury were present in 60 per cent of cases (2, 4, 5, 6, 7, 8, 9, 10 and 11) and absent in 40 per cent of cases (1, 3, 12, 13, 14 and 15). These figures are in accord with the present consensus that the absence of such signs does not preclude cardiac damage.

Mechanism of Trauma.—Penetrating injuries of the heart were recognized and considered invariably fatal for many centuries, until an increasing number of survivals evolved a syndrome which could be recognized and treated successfully. A nonpenetrating lesion does not enjoy the same clearcut recognition, and even its very existence is doubted.

Clinical reports,[11] laboratory data[12] and the files of the medical examiner of any large city offer ample proof that fatal and nonfatal cardiac damage may result after this type of injury. Postmortem examination of persons killed in automobile accidents often reveals incidental acute cardiac lesions which were not responsible for death.[13] In many survival experiments the animals used as subjects showed objective traumatic lesions. In case 6 autopsy revealed a lesion of the left ventricle, the nature of which suggested a traumatic origin.

During this type of injury the heart may be violently thrown against the bony parts; actually be compressed; be torn from its attachments; have its chambers burst open; be jarred, as in falling; have the blood forced back into the ventricles or prevented from leaving by compression, thus increasing intracardiac pressure, or be bruised by fractured bones pressing against its surface. In any given case one or all of these factors may operate.

The resulting damage is a combination of structural and functional changes, which do not necessarily parallel each other. In the animal laboratory death was not always associated with extensive lesions, whereas in the survival experiments moderate and even extensive lesions were apparent, with little dysfunction. The most common findings were single or multiple lacerations, contusions, hemorrhages and ruptures, of one or all of the layers of the heart.[10] The subsequent healing took place by fibrosis and scarring. Occasionally acute dilatation was seen. The role of reflex coronary spasm was important in explaining the diffuse and disseminated pathologic and physiologic changes which sometimes followed a single blow. Moritz and Atkins stressed the similarity of the changes occurring after experimental trauma and after coronary occlusion.

In the laboratory numerous types of arrhythmia followed artificial trauma. In this group of cases fibrillation developed only in case 6.

11. (*a*) White, P. D., and Glendy, R. E., in Brahdy, L., and Kahn, S.: Trauma and Disease, Philadelphia, Lea & Febiger, 1937, p. 59. (*b*) Bright and Beck.[6] (*c*) Warburg.[8]

12. Schlomka, G.: Experimentelle Untersuchungen über den Einfluss stumpfer Brustkorbtraumen auf das Herz, Ztschr. f. d. ges. exper. Med. **93**:751, 1934. Kulbs, F.: Experimentelle Untersuchungen über Hertz und Trauma, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:678, 1939. Kulbs, F., and Strauss, L. H.: Herz und Trauma; Weitere experimentelle Untersuchungen, Klin. Wchnschr. **11**:1572, 1932. Kissane, R.; Fidler, R. S., and Korns, R. A.: Electrocardiographic Changes Following External Chest Injury to Dogs, Ann. Int. Med. **2**:907, 1937. Bright and Beck.[6] Moritz and Atkins.[10]

13. Barber, H.: Contusion of the Myocardium, Brit. M. J. **2**:520, 1940. Leinoff.[7]

This change must be accepted with reservations, since in this case there was antecedent mitral stenosis. In case 8 there was an immediate slow pulse, in spite of all the outward signs of shock.

Those animals which died after experimental trauma invariably showed a marked curtailment of function immediately after the application of the offending force. This same change was observed to a greater or less degree at the bedside.

Clinical Considerations.—In this type of chest injury the heart may or may not be damaged. Minor lesions probably escape clinical detection because this condition is not suspected and proper diagnostic measures, such as serial electrocardiograms, are not taken.

The composite picture in this study closely resembled acute coronary occlusion with infarction. This is not surprising when it is realized that in both conditions the findings depend on acute myocardial changes. Signs and symptoms usually developed after the injury, just as after experimental trauma. The most common symptoms were pain, respiratory difficulty, rapid heart action, dizziness, unconsciousness and weakness. In case 5 these symptoms gradually subsided, but in most of the other cases they persisted, gradually became worse and usually ended in the clinical picture of shock and cardiovascular collapse. The objective findings were poor heart sounds; disturbances of rate and rhythm; normal blood pressure; the presence of a systolic murmur, perhaps due to a mild dilatation of the left ventricle, and electrocardiographic changes. It is possible that many of the changes observed in animals would be noted in patients if this condition was recognized early enough. These signs are dilatation, a falling arterial and a rising venous pressure, tick-tick rhythm, poor heart sounds, disturbances of conduction and rhythm, ventricular fibrillation, etc.[6] The acute picture may be further complicated by lacerations of the heart and its coverings, a hemopericardium and underlying quiescent processes, such as arteriosclerosis. The last-named factor was present to some degree in practically all cases.

After the acute phase the signs and symptoms depend on the amount of residual damage, the degree of healing and the efficiency of the reestablished circulation. Thus it can be seen that the picture is essentially the same as that in coronary occlusion and can be differentiated only by means of the history (cases 16 and 17). In cases 11 and 14 the injury probably produced only a symptomatic aggravation of a preexisting disease.

The history, which is a word picture of events before, during and after a given incident, is the most important single factor in any con-

sideration of trauma and subsequent disability. The objective changes caused by an injury may be the same as ones caused by other factors, and only the history will enable an observer to formulate an opinion as to causal relation. If the histories in this study were changed to exclude injuries, then an entirely different problem would be presented. This cannot be stressed too strongly. The history can reveal the previous cardiac health, the type of accident, the presenting and the bridging symptoms, the time and the character of the cardiac collapse, the amount of healing and the functional capacity of the injured organ. It is needless to emphasize that at present there are no objective measurements of pain, the most common cardiac disabling symptom, which can be judged only from the patient's story.

The courts should realize the importance of the history and accept all testimony which may aid in obtaining a true recital of events. The first recorded history is usually unbiased and contains all the facts and therefore should be given the most weight and consideration, since the needs of the moment and not future benefits were uppermost in the patient's mind at the time the history was given. Subsequent changes in the original story should be accepted with reservations. In the presence of conflicting medical histories lay witnesses should be used to determine just what happened. These histories are occasionally changed through unethical guidance in order to obtain benefits. This practice could easily be discouraged if the courts would accept the first history unless unusual circumstances prevented a recital of the facts. Since the question of causal relation hinges on the history, every effort should be made to obtain the truth.

Electrocardiographic Considerations.—The basic lesion is acute cardiac damage, and therefore serial electrocardiograms should show changes immediately after the injury. Such a lesion is not constant and varies as to location, thus producing different kinds of electrocardiographic tracings. The electrocardiographic diagnosis varied in each case, suggesting pericardial or myocardial damage. The electrocardiographic changes in cases of myocardial injury at times were similar to those characteristic of typical and atypical acute coronary occlusion.

Disability.—The question of cardiac function in workers is important. Those with a moderate degree of cardiac damage probably recover without any impairment of function (case 5). However, in most of the cases reported here the patients showed a residual disability which varied from total to partial loss of efficiency. Disability is an individual problem and depends on the amount of damage, the degree of healing, the amount of recovery and probably the presence of any underlying pathologic condition.

CONCLUSIONS

1. Direct nonpenetrating injury of the chest can produce nonfatal disabling heart damage.

2. The resulting disability is due to a combination of structural and functional changes.

3. The clinical picture is that of an acute pathologic condition of the heart and closely resembles that of coronary occlusion, from which it is differentiated by the history.

4. The history is the most important single factor in determining causal relation and the subsequent degree of disability.

5. The electrocardiographic studies are important and usually show changes associated with acute lesions.

6. This clinical syndrome should be considered in the presence of any injury of the chest.

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STENOSIS OF THE INFUNDIBULUM

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Although stenosis of the pulmonary tract with transposition is one of the most common anomalies encountered in the heart, isolated stenosis of the lower bulbar orifice without transposition is relatively rare. We were able to study clinically over an extended period a patient who on postmortem examination presented this type of anomaly.

REPORT OF A CASE

Clinical Observations.—This woman was first seen by one of us (S. S.) in 1929 at the age of 25. She gave a history of heart disease since birth. She came to inquire as to the advisability of becoming pregnant. Her symptoms were slight dyspnea on exertion for years, moderate swelling of the ankles periodically and easy tiring. She had never been incapacitated because of these complaints. She had had typhoid fever in 1910 and scarlet fever with nephritis in 1916.

Examination in 1929 revealed nothing abnormal except the cardiac condition. On percussion the transverse diameter of the heart was normal. There was dulness, however, 7 cm. to the left of the midsternal line in the second interspace. In the same region were a marked systolic thrill, which was transmitted laterally and slightly upward, and a loud, rough, systolic murmur, transmitted over the entire precordium and back. There was no cyanosis or clubbing of the fingers. The arterial blood pressure was 128 mm. of mercury systolic and 80 mm. diastolic. Roentgen examination revealed the transverse diameter of the heart to be 13 cm., as compared to a transverse chest diameter of 27.5 cm. An electrocardiogram revealed an inverted P wave in lead III (fig. 1). Urinalysis showed nothing abnormal.

The diagnosis at this time was congenital heart disease with patent ductus arteriosus or interventricular septal defect. The patient was told that there was no danger if she became pregnant, and she did so within the year.

Her pregnancy was uneventful, as was her subsequent course (with the exception of an attack of "flu" in 1933 and intermittent headaches) up to May 1938. At that time she noticed fiery red spots on her legs, which faded slowly. In July she began to have chills and a fever, her temperature ranging from 100 to 102 F. These symptoms were accompanied by a feeling of malaise and general aches and pains, as well as some joint pains. In August pains appeared in the chest on the left side, unaccompanied by cough or expectoration. At this time the patient entered the hospital.

This investigation was aided by a grant from the Otto Baer Fund.

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On admission the cardiac findings were the same as in previous years except that the heart was enlarged to the left and the second heart sound was almost inaudible at the base of the left lung. Petechiae were present in the skin of the legs. There were signs of an infarct in the upper lobe of the left lung posteriorly. The liver was palpable 3 fingerbreadths below the costal margin. The

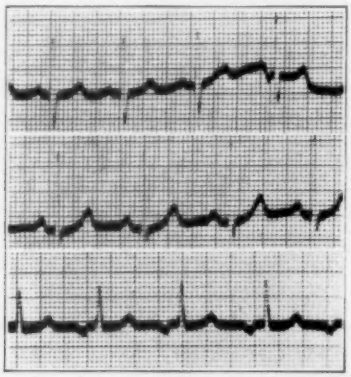

Fig. 1.—Electrocardiogram made on Dec. 17, 1929 (about ten years before death). The only possible abnormality is the inverted P wave in lead III.

Fig. 2.—Teleoroentgenogram made on Aug. 29, 1938 (about one-half year before death). The heart is enlarged; the right border is accentuated, and the left lower pulmonary field is somewhat clouded.

arterial blood pressure was 116 mm. of mercury systolic and 74 mm. diastolic. The erythrocyte count on admission was 4,700,000 per cubic millimeter, which progressively decreased to 3,900,000. The hemoglobin was 80 to 70 per cent. The leukocyte count increased from 8,200 to 15,000 per cubic millimeter, with 60 per cent polymorphonuclear leukocytes. Blood cultures were repeatedly positive for Streptococcus viridans. The urine showed occasional red and white blood corpuscles. A roentgenogram taken August 29 (fig. 2) revealed an enlarged

heart with a prominent right auricle and a probable pulmonary infarct in the lower lobe of the left lung.

The diagnosis at that time was subacute bacterial endocarditis (Str. viridans) engrafted on a congenital cardiac lesion, probably a patent ductus arteriosus.

During the first week of the patient's stay in the hospital a septic temperature was sustained. The temperature then leveled off for two weeks, only to assume again a febrile, although not typically septic, course, with temperatures ranging between 99 and 101 F. Two weeks after admission sulfanilamide therapy was started. An adequate concentration of sulfanilamide in the blood was reached and was maintained for ten days, but the temperature remained elevated and the blood culture positive for Str. viridans. Sodium cacodylate therapy also failed to influence the course of the disease. On September 24 another small pulmonary infarct occurred, and on October 2 the presence of a small cerebral embolus was suspected.

The patient left the hospital on October 15 in fairly good condition with a low grade fever and remained at home in bed. Her course was gradually downhill. From time to time the urine showed erythrocytes and leukocytes. In April 1939 these became much more numerous. At this time she became nauseated and vomited and became dyspneic and somewhat stuporous.

She reentered the hospital on May 15. At this time numerous petechiae were present. The eyelids were puffy. The cardiac findings were the same as previously except that now for the first time a soft, blowing diastolic murmur was heard along the left border of the sternum in the second and the third interspace. The liver extended 4 fingerbreadths below the costal margin on deep inspiration. The spleen was distinctly palpable. There were marked generalized redness, especially over the legs and thighs, and generalized peripheral edema. The urine contained albumin (3 plus), many leukocytes and erythrocytes and an occasional cast. The arterial blood pressure was 118 mm. of mercury systolic and 60 mm. diastolic. The nonprotein nitrogen content of the blood on admission was 82 mg. per hundred cubic centimeters, 118 mg. on May 20 and 120 mg. on May 24. with a creatinine content of 5.4 mg. per hundred cubic centimeters. On May 2- and 25 the patient experienced convulsive seizures involving the right side of the face and the right extremities, with loss of consciousness. On May 26 she died suddenly.

The diagnosis at this time, in addition to the previous diagnosis, was nephritis (focal or diffuse) secondary to bacterial endocarditis. Because of the appearance of a diastolic murmur, the congenital lesion was thought to be a patent ductus arteriosus.

Postmortem Examination.—Aside from the condition in the heart, the pathologic diagnosis included (1) subacute splenic hyperplasia; (2) chronic passive hyperemia of the lungs, liver, spleen and kidneys; (3) bilateral hydrothorax, ascites and peripheral edema and (4) acute glomerulonephritis superimposed on a subacute diffuse form of this disorder.

The heart was enlarged, weighing 450 Gm. The arterial trunks emerged in their normal positions. The conus of the right ventricle was bulging and was distinctly demarcated from the right ventricle proper. Its lower portion formed an aneurysmal dilatation measuring 3 cm. in its greatest diameter. The epicardium was dull, granular and covered with fibrin.

The right auricle was dilated and its wall thickened, measuring 1.5 mm. in width. The foramen ovale was closed. The tricuspid orifice was dilated and measured 11 cm. in circumference. The tricuspid valve was normally formed.

However, a firm band extended from the medial end of the anterior leaflet to the firm circular fibrous band to be described. This band had demobilized this portion of the leaflet. The posterior papillary muscle was large, and the anterolateral muscle was relatively small. The mural and the luminal aspects of the anterior leaflet were covered with luxuriant, reddish yellow, semifirm vegetations. Similar smaller and more discrete vegetations were present on the luminal aspect of the medial and the inferior leaflet. Some of the chordae of the anterior leaflet were firm and fibrous.

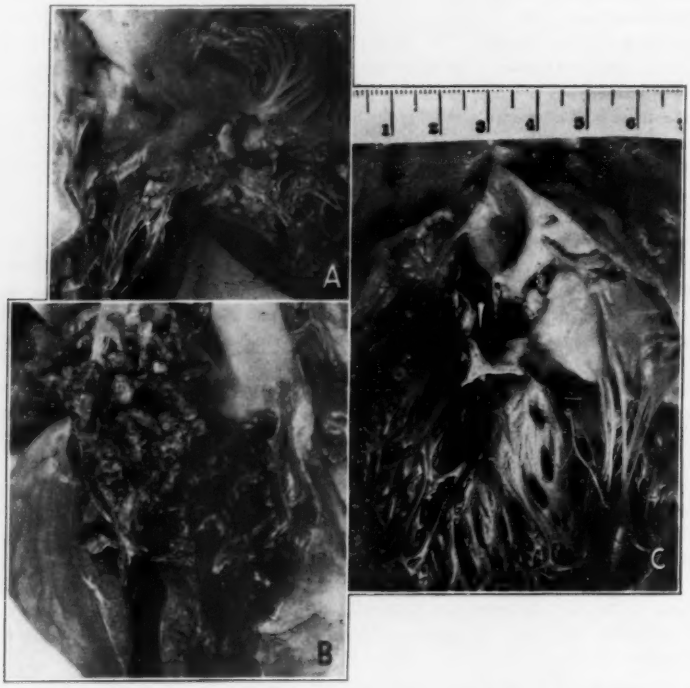

Fig. 3.—*A*, right auricular and ventricular view. Note the vegetations on the tricuspid valve. *B*, right ventricular and infundibular view. The whole infundibulum is filled with vegetations. It is separated from the sinus of the right ventricle by a fibromuscular band, which has been cut into. *C*, left ventricular view. Note that the pars membranacea is markedly thickened. Its inferior border is rolled up to form a systolic pocket. The triangular white rod extends into the defect in the pars membranacea.

The right ventricle was divided into two separate chambers—a superior infundibular outlet portion leading into the pulmonary artery and an inferior main inlet portion communicating with the tricuspid orifice. This division was produced by a firm fibrous band which extended from a point immediately below

the defect in the interventricular septum to be described, in a horizontal direction over the anterior wall of the left ventricle 1 cm. above the anterior leaflet of the tricuspid valve, then back to the septum 1 cm. above the muscle of Lancisi. The lumen produced by this ring measured 1 cm. in diameter.

The lumen of the inferior right ventricular chamber was moderate in size. Its wall, however, was thickened, measuring 0.8 cm. in width. The trabeculae carneae in this chamber were markedly accentuated. The septal muscle bundle began in its usual anterolateral origin and ascended the interventricular septum obliquely to the fibrous ring. It passed behind this ring to continue its course in the superior right ventricular chamber.

The superior infundibular right ventricular chamber was of moderate size. Its wall measured 3 mm. in thickness. The chamber was completely filled with luxuriant vegetations, which had produced the bulge seen externally in the region of the conus. These vegetations were closely adherent to the mural endocardium and to the fibrous ring, where they became continuous with those covering the mural aspect of the anterior tricuspid leaflet, and superiorly to both aspects of the pulmonic valve, extending into the pulmonary artery for a distance of 5 cm. A separate large vegetation lay lodged in the terminal portion of the right pulmonary artery. On removal of the vegetations the remainder of the topography of the muscle bundles of the right ventricle could be discerned. The septal muscle bundle terminated at the base of the septal cusp of the pulmonic valve. The parietal muscle bundle, however, was relatively short, joined the septal muscle bundle at the raphe at the base of the pulmonic valve and terminated inferiorly after a 2 cm. excursion in a well formed recess. The remainder of the anterior wall of the conus could not be well discerned because of the markedly thickened endocardium covered by adherent vegetations.

The pulmonic valve and orifice were normal, and the two pulmonary arteries were given off normally. The ductus arteriosus was closed.

The pulmonary veins and the left auricle were normal. The mitral orifice measured 7.5 cm. in circumference. There were several small, confluent, yellowish gray, granular excrescences at the line of juncture between the anterior and the inferior leaflet of the mitral valve, and several grayish white, smooth, well circumscribed, thickened patches were occasionally encountered.

The left ventricular wall measured 0.9 cm. in greatest thickness. The left ventricular cavity was small in comparison to that of the right ventricle. The pars membranacea was thickened, grayish white and smooth. This thickened region extended upward to involve the right anterior aortic cusp, the posterior basal part of which showed a large, well circumscribed, firm, grayish white, smooth plaque. One millimeter from the base of the right anterior aortic cusp was a defect in the pars membranacea measuring 1 mm. in diameter. From this defect protruded a grayish yellow, friable vegetation.

The aortic orifice measured 5 cm. in diameter. The corpus arantii of each aortic cusp was the seat of a friable, yellowish gray, polypoid vegetation. The aorta was narrow throughout its course. The lining of the aorta was singularly free from plaques. The coronary vessels presented no abnormality.

Microscopically, the myocardium showed marked granular and fatty degeneration. The epicardium presented a thick, fibrinous layer containing clusters of round cells. The vegetations showed many bacteria.

A culture of blood drawn post mortem revealed streptococci (the type could not be subcultured) and Bacillus coli.

As far as the heart is concerned the diagnosis included the following conditions: 1. Congenital malformation of the heart, with (*a*) stenosis of the lower infundibular ostium, (*b*) patent interventricular septum in the region of the pars membranacea and (*c*) hypertrophy of the right ventricle proximal to the infundibulum. 2. Acute vegetative endocarditis involving the infundibular portion of the right ventricle; the pulmonic, tricuspid, mitral and aortic valves; the main pulmonary artery, and the endocardium surrounding the opening in the interventricular septum. 3. Acute fibrinous pericarditis. 4. Embolic occlusion of the orifice of the right pulmonary artery by large vegetations and multiple embolic occlusions of the smaller radicles, with the formation of a mycotic aneurysm.

Comment.—In retrospect, it is difficult to see how the diagnosis of the cardiac lesion could have been made. When the patient was first seen, ten years before death, a systolic murmur was heard at the base of the left lung. This could have been ascribed to a defect of the interventricular septum, pulmonary stenosis or a patent ductus arteriosus, which may produce only a systolic murmur. In the absence of cyanosis and clubbing and in the absence of a diminution of the P wave in lead II, we did not think we were dealing with pulmonary stenosis. Therefore, in view of the type of murmur, the most likely diagnosis was an interventricular septal defect.

When the patient was seen ten years later, the P wave in lead II was distinctly diminished. In view of the fact that the patient then had subacute bacterial endocarditis and evidence of failure of the muscle on the right side of the heart, the diminution was considered to be due to the failure of this muscle. Thus, the diagnosis still was an interventricular septal defect. On the last admission the appearance of a diastolic murmur in the same region as the systolic murmur still further complicated the picture and made us veer toward the diagnosis of a patent ductus arteriosus.

It is of interest that the patient toward the end of her illness showed signs of uremia. A clinical diagnosis of nephritis secondary to bacterial endocarditis was made, no distinction being drawn between focal and diffuse glomerulonephritis. A diagnosis of diffuse glomerulonephritis might have been more exact, for focal glomerulonephritis (multiple glomerular embolization) is most often not accompanied by an impairment of renal function. Only a few cases of marked glomerular embolization with resultant impairment of renal function have been reported (Bell [1])

The sudden death of the patient was well explained at postmortem examination by the presence of the large vegetation blocking the right main pulmonary artery.

There remains to be explained the diastolic murmur heard at the base of the left lung on the patient's second admission. The pathologic

1. Bell, E. T.: Am. J. Path. **8**:639, 1932.

findings do not clearly account for this murmur. There was a thickening of the base and the body of the right anterior aortic leaflet, as well as vegetations on the valve. Whether this led to a mild aortic regurgitation cannot definitely be stated. It is also possible that terminally there might have been some pulmonary insufficiency due to the dilated pulmonary ring and the involvement of the valve by vegetations.

Summary.—A 35 year old woman had congenital heart disease, subacute bacterial endocarditis and acute and subacute glomerulonephritis. The cardiac abnormality consisted of infundibular stenosis with a defect of the interventricular septum. The endocarditis probably began on the defect and spread to the conus. The patient died from the combined effects of heart failure, uremia and toxemia and, finally, from the lodging of a huge vegetative embolus in the right main pulmonary artery.

ANATOMIC AND PATHOGENETIC CONSIDERATIONS

From the anatomic standpoint there are various types of conus stenosis, dependent on the size of the infundibulum and the point of stenosis (Keith,[2] Abbott [3] and others). 1. In the least common type (occurring in 19 of 100 cases reported by Keith [2]) the conus is separated from the sinus of the right ventricle by a fibromuscular septum, resulting in two distinct chambers. The point of stenosis is thus at the lower bulbar orifice at the point of junction with the sinus of the right ventricle. About 60 cases of this anomaly have been reported in the literature. 2. In a second group there is an arrest in development of the infundibulum. The infundibular cavity is small and communicates with the sinus of the right ventricle by a small ostium. This is a more common type than the first (occurring in 44 of 100 cases reported by Keith [2]). 3. In the third type there is an almost complete absence of the infundibulum. This is also relatively common.

In almost all cases of the second or the third type of anomaly it is accompanied by transposition. When the stenosis is limited to the lower bulbar orifice, it is more commonly associated with transposition. In the few cases in which transposition does not occur, there is most frequently an accompanying defect or an aneurysm of the interventricular septum. Infundibular stenosis with closed fetal passages is rare.

In the heart we have described it is apparent we are dealing with stenosis of the conus at the lower bulbar ostium with an interventricular septal defect, without transposition of the large arteries.

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The various theories propounded as the cause of all types of conus stenosis do not fall within the scope of this report. (see Spitzer,[4] Pernkopf and Wirtinger,[5] and Lev and Saphir [6]). In the isolated type of conus stenosis (without transposition), we must assume that the movements of the heart during the absorption of the bulbus proceeded normally. However, the incorporation of the pulmonic portion of the bulbus into the right ventricle was faulty.

As in our case, most patients with conus stenosis survive to adulthood. When the stenosis is part of a tetralogy, then the patients may die from heart failure. However, many patients with an anomaly of this type and most patients with the isolated type of stenosis die from bacterial endocarditis (Harrison,[7] Eakin and Abbott [8] and Abbott [8]). The vegetations are usually especially luxuriant, as in our case. This has been commented on by Abbott, Harrison and others. No reason has as yet been advanced for the great luxuriance of endocarditic vegetations on the right side of the heart. In 2 cases (1 reported by Clarke [9] and ours), some of these vegetations broke off and produced large pulmonary emboli, blocking the main pulmonary arteries.

SUMMARY

A case of infundibular stenosis without transposition is presented from the clinical and the pathologic standpoint. The various types of infundibular stenosis are discussed, and the various theories concerning the pathogenesis of this anomaly are reviewed.

Infundibular stenosis is most frequently part of a tetralogy of Fallot and as such represents the result of an abnormality both in the absorption of the bulbus and in its incorporation into the right ventricle. When stenosis is present without transposition, the absorption of the bulbus must have proceeded normally but its final incorporation into the right ventricle must have been faulty.

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RENAL FUNCTION IN DIABETES INSIPIDUS

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Diabetes insipidus and the mechanism of its underlying disturbance have long been a source of interest to investigators. During the last two to three decades a considerable literature has developed along various lines of approach, such as the central nervous system, the endocrine system, the body metabolism and the kidney. It is the last of these that is of particular interest, with specific regard to renal hemodynamics, water exchange and the relation of both to the pituitary.

REVIEW OF LITERATURE

These three aforementioned aspects of renal function, both in physiologically normal persons and in patients with diabetes insipidus, can be resolved into several fundamental questions: 1. To what extent is the amount of urine excreted a function of (*a*) renal blood flow or (*b*) glomerular filtration? 2. (*a*) What is the relation of the pituitary to urine output as regards both diuresis and antidiuresis? (*b*) Is the mechanism of its action renal or extrarenal? (*c*) If the mechanism is renal, to what extent do renal blood flow, glomerular filtration and tubular function play a role?

Urine Output.—Relation of Amount of Urine Excreted to Renal Blood Flow: With the Rein [1] thermostromuhr as a means of measuring renal blood flow, Janssen and Rein,[2] using decerebrate dogs, could find no relation between renal blood flow and urine output, while Samaan and Handovsky,[3] using conscious dogs, found that after administration

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This study was aided by the fund for study of renal vascular disease.

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(Footnote continued on next page)

of water an increase in the renal blood flow preceded an increase in urine output. Schmidt and Walker [4] and Walker and associates [5] were in agreement with Janssen and Rein. Van Slyke, Rhoads, Hiller and Alving,[6] using the urea excretion method in dogs, and Chasis, Ranges, Goldring and Smith,[7] using diodrast clearance as a measure of effective renal blood flow in normal human subjects, reported that no relation existed.

Urine Output and Glomerular Filtration: The possibility that diuresis could be attributed to an altered rate of glomerular filtration was studied in dogs by means of creatinine clearance as a measure of glomerular filtration by Marshall,[8] Poulsson [9] and Walker and associates,[5] while Chasis and co-workers [7] studied this question in human subjects by means of inulin clearance. No relation between urine output and glomerular filtration rate could be detected by these observers. This is in contrast to the results of Kaplan and Smith,[10] who reported a corresponding change in urine output and glomerular filtration rate in rabbits. In conclusion, it is apparent that the predominance of opinion does not favor a relation between either renal blood flow or rate of glomerular filtration and urine output in the normal physiologic state.

Relation of the Pituitary to Urine Output.—Diuresis and Antidiuresis: The first widely accepted action of pituitary extract was the diuretic effect on the kidney, originally reported in 1901 by Magnus

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and Schäfer [11] and later by Schäfer.[12] Recently Heller [13] reviewed this subject and the role of anesthesia in the production of the diuretic effect and reported the separation of the pressor fraction from the antidiuretic factor. He showed that the pressor substance alone is responsible for the diuresis, the effect being of vascular origin, much like that of epinephrine reported by Richards and Plant.[14]

The antidiuretic properties of posterior pituitary extract were not recognized until Frank [15] in 1912 noted an association between injuries to the hypophysis and the state of diabetes insipidus. Simmonds [16] reported 3 cases of polyuria following destruction of the posterior lobe of the pituitary, and Goldzieher,[17] 2 cases. Van der Velden [18] and Farini [19] independently demonstrated the use of posterior pituitary extract in producing antidiuresis. That the same effect could be produced in normal water diuresis was successively demonstrated both in animals and in human subjects by Konschegg and Schuster,[20] Motzfeldt,[21] Rees,[22] Priestley [23] and Weir, Larson and Rowntree.[24]

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Renal or Extrarenal Mechanism of the Antidiuresis Caused by Administered Posterior Pituitary Extract: It appears that there may be three ways in which the pituitary extract may act in inhibiting urine output. 1. It might affect the water exchange between blood and tissues. This is most easily ruled out, since, first, there is no evidence favoring it and, second, it should actually stimulate diuresis on the basis of plasma dilution (Poulsson,[25] Priestley,[22] Craig,[26] and Underhill and Pack[27]). 2. It might act indirectly through the nervous system and tissues by way of a hypothalamic regulating center, advocated largely by the Viennese school (Molitor and Pick,[28] Mehes and Molitor[29] and Hoff and Wermer[30]). This still requires confirmation. 3. It might act directly on the kidney. This hypothesis was supported by the heart-lung-kidney preparation of Starling and Verney,[31] in which the urine showed the characteristic changes which occur after administration of pituitary extract. It was also supported by the results of Janssen,[32] who showed that direct injection of pituitary extract into the renal artery of one kidney produced a response in that kidney before a similar response occurred in the opposite kidney. This effect was produced despite the ruling out of a nervous mechanism by section of the spinal nerves between the fifth and the sixth cervical vertebra and double vagotomy. This was also corroborated by Verney,[33] Klisiecki and associates[34] and Theobald.[35]

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32. Janssen, S.: Ueber zentrale Wasserregulation und Hypophysenantidiurese, Arch. f. exper. Path. u. Pharmakol. **135**:1, 1928.

33. Verney, E. B.: (*a*) The Secretion of Pituitrin in Mammals, as Shown by Perfusion of the Isolated Kidney of the Dog, Proc. Roy. Soc., London, s.B **99**:487,

(Footnotes continued on next page)

From still another angle, McIntyre and Van Dyke [36] by a study of the chloride and the bromide distribution between cells and plasma under different conditions controverted the extrarenal mechanism.

Role of Renal Blood Flow, Glomerulus and Tubule Cell in the Production of Antidiuresis: Renal blood flow. Earlier work by Dale,[37] Motzfeldt,[21] King and Stoland,[38] Knowlton and Silverman,[39] Richards and Plant,[14] Priestley [23] and Abel and Geiling [40] produced varying results, with no conclusive evidence that the circulatory mechanism was responsible for antidiuresis, though at times the results were suggestive. Starling and Verney,[31] too, using the isolated perfused kidney, could not attribute the antidiuresis to a vascular effect. Later studies emphasized this. Brings and Molitor [41] noted an initial reduction in the renal volume, which passed off long before the antidiuretic effect. Geiling, Herrick and Essex,[42] Herrick [43] and Walker and associates [5] noted a transient diminution followed by an actual increase in renal blood flow. Samaan and Handovsky [3] apparently made the same observation, disagreeing only in relation to water diuresis, contrary to the citation by

1926; (*b*) Die Wasserausscheidung der Säugetierniere und ihre physiologische Regulation, Arch. f. exper. Path. u. Pharmakol. **181**:24, 1936.

34. Klisiecki, A.; Pickford, M.; Rothschild, P., and Verney, E. B.: The Absorption and Excretion of Water by the Mammal: I. The Relation Between Absorption of Water and Its Excretion by the Innervated and Denervated Dog, Proc. Roy. Soc., London, s.B **112**:496, 1933.

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36. McIntyre, A. R., and Van Dyke, H. B.: The Distribution and Concentrations of Water and Halides in the Blood and Urine During Diuresis-Inhibition by Pituitary Extract, J. Pharmacol. & Exper. Therap. **42**:155, 1931.

37. Dale, H. H.: The Action of Extracts of the Pituitary Body, Biochem. J. **4**:427, 1909.

38. King, C. E., and Stoland, O. O.: The Effect of Pituitary Extract on Renal Activity, Am. J. Physiol. **32**:405, 1913-1914.

39. Knowlton, F. P., and Silverman, A. C.: The Activity of Pituitary Extract on the Kidney, Am. J. Physiol. **47**:1, 1918.

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41. Brings, L., and Molitor, H.: Ueber die Beziehungen zwischen onkometrisch verzeichneten Groszenänerungen der Niere und Diurese nach Versuchen an der verlagenten Niere, Arch. f. exper. Path. u. Pharmakol. **159**:710, 1931.

42. Geiling, E. M. K.; Herrick, J. F., and Essex, H. E.: The Effect of Posterior Pituitary Preparation on the Blood Flow of the Normal Intact Dog, J. Pharmacol. & Exper. Therap. **51**:18, 1934.

43. Herrick, J. F. (1938), cited by Corcoran and Page.[45]

Walker and associates [5] and Smith.[44] Corcoran and Page,[45] after measuring renal blood flow indirectly by a modification of the method of Van Slyke and co-workers [6] in which phenolsulfonphthalein (Sheehan [46]) and inulin were used instead of urea, reported a rise in 5 animals and a fall in 4. They could offer no explanation for the inconsistent results. Therefore, the few experiments to the contrary notwithstanding, the effect of pituitary extract on the renal hemodynamics is but transient and cannot account for prolonged antidiuresis.

The glomerulus. Richards and Plant [14] early showed in the rabbit kidney that small doses of solution of posterior pituitary will produce an actual increase in urine output by constricting the efferent arteriole and thereby increasing the intraglomerular pressure. Larger doses, however, produce anuria by also constricting the afferent arteriole. Adolf [47] made similar observations. More elaborate information was sought by the application of clearance tests. Poulsson [25] and Walker and co-workers,[5] using creatinine clearance, and Burgess, Harvey and Marshall,[48] using the xylose and sucrose method of Shannon, Jolliffe and Smith,[49] failed to note any significant decrease in glomerular filtration either in dogs or in human subjects after the administration of solution of posterior pituitary. Gersch,[50] using the ferrocyanide method, was in agreement. Corcoran and Page,[45] on the other hand, employing inulin clearance, noted an increase in the rate of glomerular filtration in the periods of decreased renal blood flow, which suggested constriction of the efferent arterioles. Therefore, from previous evidence one could hardly attribute antidiuresis to an alteration in glomerular function. Special note must be made that apart from the last-named authors, no

44. Smith, H. W.: Physiology of the Renal Circulation, in Harvey Lectures, 1939-1940, Baltimore, Williams & Wilkins Company, 1940, pp. 166-222.

45. Corcoran, A. C., and Page, I. H.: The Effects of Renin, Pitressin and Pitressin and Atropine on Renal Blood Flow and Clearance, Am. J. Physiol. **126**: 354, 1939.

46. Sheehan, H. L.: The Renal Elimination of Phenol Red in the Dog, J. Physiol. **87**:237, 1936.

47. Adolf, E. F.: How Pituitrin Inhibits Urine Formation, Am. J. Physiol. **116**:1, 1936.

48. Burgess, W. W.; Harvey, A. M., and Marshall, E. K., Jr.: The Site of Antidiuretic Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **49**:237, 1933.

49. Shannon, J. A.; Jolliffe, N., and Smith, H. W.: The Excretion of Urine in the Dog: VI. The Filtration and Excretion of Exogenous Creatinine, Am. J. Physiol. **102**:534, 1932.

50. Gersch, I.: Reabsorption of Water During Pituitary Anti-Diuresis, J. Pharmacol. & Exper. Therap. **52**:231, 1934.

investigator has been able to obtain positive evidence for an effect of pituitary extract on glomerular function by means of clearance methods.

The tubule cell. Addis and associates [51] early postulated that the inhibitory effect of pituitary extract was due to its specific action on the secreting cell of the kidney. Positive evidence, especially for the proximal portion of the tubule as the site of antidiuretic action, was proposed by Poulsson [25] on the basis of the effect of pituitary extract on urea excretion. Gersch and Stieglitz [52] and Gersch,[50] using the ferrocyanide method, stipulated the loop of Henle, and less so the proximal convolutions, as the site of action, as did Burgess, Harvey and Marshall [48] in their comparative zoologic study of antidiuretic response. The evidence, therefore, favors the position that the pituitary exerts its antidiuretic action on the kidney by its specific effect on the tubule cell.

Renal Function Under Conditions of Pituitary Deficiency.—However indefinite is present knowledge of renal physiology in regard to the response of the kidney to administered pituitary extract, all the more uncertain is it when the organism is deprived of that influence. Knowledge of this phase of renal behavior is essential to the better understanding of diabetes insipidus.

Schmitz [53] found the creatinine clearance in 4 cases of diabetes insipidus to be normal and concluded that polyuria is due to a failure in tubular reabsorption of water. White and Heinbecker [54] studied renal function in dogs in which the pars nervosa of the pituitary and the accessory sites of pitressin production were removed. Within two to four weeks after operation they noted a fall both in urea and in creatinine clearance from 30 to 50 per cent, with a return to normal after several months. In later experiments,[55] they noted that the fall in urea clearance was less than that of creatinine clearance and might not fall at all.

51. Addis, T.; Shevky, A. F., and Bevier, G.: The Regulation of Renal Activity: VII. The Balance Between the Regulation by Adrenalin and by Pituitrin, Am. J. Physiol. **46**:129, 1918.

52. Gersch, I., and Stieglitz, E. J.: Histochemical Studies of the Mammalian Kidney: I. The Glomerular Elimination of Ferrocyanide in the Rabbit and Some Related Problems, Anat. Rec. **58**:349, 1934.

53. Schmitz, H. L.: The Mechanism of Human Diabetes Insipidus, J. Clin. Investigation **16**:675, 1937.

54. White, H. L., and Heinbecker, P.: Hypophyseal Influences in Renal Function and Water Exchange in the Dog, Am. J. Physiol. **123**:213, 1938.

55. White, H. L., and Heinbecker, P.: Observations on Creatinine and Urea Clearances on Responses to Water Ingestion and on Concentrating Power of Kidneys in Normal, Diabetes Insipidus and Hypophysectomized Dogs, Am. J. Physiol. **123**:566, 1938.

Recently these same authors with an associate [56] carried on studies more closely related to those presented here. In their earlier studies White and Heinbecker [56a] measured the renal function in 2 hypophysectomized dogs by means of inulin and diodrast clearances. They observed both clearances to be one half those found in the normal dog and postulated that though they did not determine the total tubular excretory mass (T_m), it, too, was probably one half of normal. In their most recent report White, Heinbecker and Rolf [56b] recorded their observations on 6 hypophysectomized dogs. The diodrast plasma clearance after operation showed an average decrease of more than 40 per cent, with an approximately corresponding drop in the renal plasma flow. Both the plasma diodrast extraction determined from blood drawn from the renal vein and tubular diodrast extraction remained constant in the normal and in the hypophysectomized animals. The glomerular filtration rate decreased correspondingly with the drop in renal plasma flow, while the filtration fraction remained unchanged. The total excretory mass after hypophysectomy was found to be decreased by more than 50 per cent. The total blood volume was decreased by 20 per cent. In view of the unchanged tubular extraction of diodrast at a low plasma level in the face of a definitely decreased total excretory mass, the authors postulated some hypothetic substance concerned in the tubular excretion of diodrast to be deficient in quantity but not in quality. The fall in renal plasma flow is attributed to a combination of a fall in blood volume, diminished cardiac output and uniform renal vasoconstriction.

PURPOSE OF STUDY

It was with the application of the inulin and of the diodrast clearance test that the problem of the function of the kidney in diabetes insipidus in human beings was approached. It was hoped, thereby, to shed light on the following questions: 1. What is the state of (*a*) renal blood flow, (*b*) glomerular filtration and (*c*) tubular function in the two well established phases, the untreated, or diuretic, and the treated, or antidiuretic, phase? 2. During the transition from the antidiuretic to the diuretic phase due to the progressive loss of the effect of administered posterior pituitary extract, what relation can be established between renal blood flow and glomerular filtration, on the one hand, and urine output, on the other? 3. What changes, if any, occur in the kidney in a diuretic state

56. (*a*) White, H. L., and Heinbecker, P.: Observations on Inulin and Diodrast Clearances and on Renal Plasma Flow in Normal and Hypophysectomized Dogs, Am. J. Physiol. **130**:464, 1940. (*b*) White, H. L.; Heinbecker, P., and Rolf, D.: Effects of Hypophysectomy on Some Renal Functions, Proc. Soc. Exper. Biol. & Med. **46**:44, 1941.

after a single dose of pituitary extract, with its almost instantaneous antidiuretic effect? 4. What changes occur in percentage of plasma volume during this acute transition? 5. Are there observable changes in renal blood flow after administration of water once antidiuresis is established?

MATERIAL

In an attempt to answer the foregoing questions, it was possible to study renal function in 7 males with diabetes insipidus. In 6 of them moderate to marked diuresis occurred during the untreated phase. In the seventh patient the diuresis was counteracted by thyroidectomy. A brief outline of each case follows:

CASE 1.—H. N., aged 36, had had diabetes insipidus for fifteen years. The etiology was unknown. The usual fluid intake and output was 10 to 11 liters per day. During treatment with solution of posterior pituitary [57] the fluid exchange fell to 2 to 3 liters per day. The basal metabolic rate was —16 per cent. Except for being somewhat underweight, the patient was essentially normal on physical examination. At the time of this study he was taking solution of posterior pituitary regularly.

CASE 2.—S. T., aged 24, had had diabetes insipidus since early childhood. The etiology was unknown. The fluid intake and output was 11 to 12 liters per day; during treatment with posterior pituitary the fluid exchange decreased to 3 liters. On physical examination the patient appeared essentially normal. At the time of this study he was not taking solution of posterior pituitary regularly.

CASE 3.—F. C., aged 35, had an illness of eleven years' duration which was believed to have followed a streptococcic infection of the throat. The fluid intake and output was 10 to 11 liters per day; during treatment with posterior pituitary the fluid exchange fell to 2 liters. On physical examination the patient was essentially normal. At the time of this study he was not taking posterior pituitary extract regularly, since it induced asthmatic seizures.

CASE 4.—R. D., aged 32, had had diabetes insipidus of unknown etiology for four years. The fluid intake and output was about 10 liters per day; during treatment with pituitary extract the fluid exchange fell to 2 to 3 liters. On physical examination the patient was essentially normal. At the time of this study the patient was not taking solution of posterior pituitary regularly

CASE 5.—G. A., aged 13, had an illness of four years' duration which was believed to have followed an infection of the middle ear. The fluid intake and output was 10 to 15 liters per day. During treatment with solution of posterior pituitary the fluid exchange decreased to 2 to 3 liters. The patient's growth was moderately stunted, but otherwise physical examination revealed nothing abnormal. At the time of this study he was taking pituitary extract regularly.

CASE 6.—J. K., aged 28, had an illness of nine years' duration of unknown etiology. The fluid intake and output was 8 to 11 liters per day, though shortly before this study it decreased to 6 liters per day. During treatment with solution of posterior pituitary the fluid exchange fell to 2 liters per day. The basal

57. In all cases during medication and/or experimental procedure solution of posterior pituitary U. S. P. was used.

metabolic rate was —21 per cent. Moderate underdevelopment of the genitalia was present, but otherwise physical examination revealed nothing abnormal. At the time of this study the patient was taking posterior pituitary extract regularly.

CASE 7.—L. R., aged 35, had postencephalitis with parkinsonism and diabetes insipidus of ten years' duration. The fluid intake and output was originally 8 to 10 liters per day. Total thyroidectomy done six years ago was accompanied by a reduction in fluid exchange to 3 liters per day. During the six year period the weight increased from 113 to 203 pounds (51 to 92 Kg.). The basal metabolic rate was —25 per cent.

METHOD

Renal blood flow was determined indirectly by measuring the effective plasma clearance of diodrast divided by the percentage of plasma volume, as described by Smith, Goldring and Chasis [58] and Chasis, Ranges, Goldring and Smith.[7] The method essentially depends on the clearance of a substance that is entirely excreted through the glomeruli and tubules in one circulation of renal arterial blood. Maximum clearance is obtained at such plasma concentrations that the ratio of tubular excretion is in direct proportion to the plasma concentration—usually less than 5 mg. per hundred cubic centimeters. Iodine determinations were carried out according to the Smith modification [58] of the Kendall method.[59] The glomerular filtration rate was determined by measuring inulin clearance on the principle that inulin is completely filtered through the glomerulus and only by the glomerulus.[60] The determination of inulin was done according to the method of Alving, Rubin and Miller [61] and their later modification.[62] The total tubular excretory mass (T_m) was determined at raised plasma diodrast concentrations,[58] under which circumstance tubular excretion is independent of glomerular activity and renal blood flow and is proportional to the number or mass of actively excreting tubules. It is to be noted that all figures are calculated on the basis of a standard surface area of 1.73 square meters.

In the experiments presented here, the infusions of inulin alone and diodrast in physiologic solution of sodium chloride were prepared in such concentrations

58. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263, 1938.

59. Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity: III, J. Biol. Chem. **43**:149, 1920.

60. Shannon, J. A., and Smith, H. W.: The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, J. Clin. Investigation **14**:393, 1935. Shannon, J. A.: The Excretion of Inulin by the Dog, Am. J. Physiol. **112**:405, 1935; The Excretion of Inulin and Creatinine at Low Urine Flows by the Normal Dog, ibid. **114**:362, 1936. Hendrix, J. P.; Westfall, B. B., and Richards, A. K.: Quantitative Studies of Composition of Glomerular Urine: XIV. The Glomerular Excretion of Inulin in Frogs and Necturi, J. Biol. Chem. **116**:735, 1936. Richards, A. N.; Bott, P. A., and Westfall, B. B.: Experiments Concerning the Possibility That Inulin Is Secreted by the Renal Tubules, Am. J. Physiol. **123**:28, 1938. Smith, Goldring and Chasis.[58] Chasis, Ranges, Goldring and Smith.[7]

61. Alving, A. S.; Rubin, J., and Miller, B. F.: A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, J. Biol. Chem. **127**:609, 1939.

62. Personal communication to the author.

as to give a plasma iodine level of approximately 2 mg. per hundred cubic centimeters in the determination of effective plasma clearance and 30 mg. per hundred cubic centimeters or higher in the determination of the total excretory mass and a plasma inulin level of approximately 10 mg. per hundred cubic centimeters throughout the experiment to determine glomerular filtration rate. The infusion was given intravenously at an average rate of 4 to 5 cc. per minute for twenty to thirty minutes before study to insure equilibrium.

Preparation of Patients.—Before any studies were done, these patients were first prepared according to certain routine procedures. (*a*) A period of hydration of three to four days preceded all experiments. Patients not taking posterior pituitary extract were encouraged to drink abundantly and on the morning of the experiment to drink 1.5 to 3 liters up to ninety minutes before study. This was regarded as essential to counteract possible dehydration. Those patients receiving pituitary extract were also encouraged to take fluids over this same period, though to a more moderate degree, including 1 to 1.5 liters the morning of study. (*b*) The diuretic phase was established in those patients taking posterior pituitary extract regularly by depriving them of the extract for a minimum of two to three days, till maximum diuresis was attained. In later experiments, this period of deprivation was prolonged to one week. (*c*) In giving pituitary extract to a patient not taking it regularly a solution of posterior pituitary was administered for three days preceding the experiment in 1 cc. doses subcutaneously,[63] with a minimum of three doses the first day, two the second day and one the morning of the experiment, at which time the antidiuretic effect was well established.

RESULTS

Renal Function in Established Diuresis and Antidiuresis.—The comments on this study can be best made as analyses of individual behavior (table 1).

Case 1.—The effective plasma clearance on two occasions, following diuresis of seven and, essentially,[64] eighteen days' duration, respectively, was decreased 50 or more per cent compared with that after treatment with posterior pituitary extract for two weeks. On the other hand, after diuresis of two and a half to three days' duration, there was no diminution in clearance. Both the total excretory mass and the glomerular filtration rate were practically constant in all three experiments.

Case 2.—Effective plasma clearance during the diuretic phase was decreased on the first occasion by 60 per cent and on the second occasion by 30 per cent compared with that after treatment with posterior pituitary extract. In this case also the glomerular filtration rate and the total excretory mass were essentially unchanged.

Case 3.—On first examination the effective plasma clearance was decreased by 40 per cent compared with that after four days' treatment with posterior pituitary extract. Another study during the diuretic phase revealed a clearance decreased by only 20 per cent. At this time, however, the urine output was only 3.1 cc per minute, which is no greater than that of a nondiabetic person

63. In case 5 the pituitary extract was administered intranasally.

64. The patient took one dose of posterior pituitary extract ten days before study.

TABLE 1.—*Effect of Repeated Administration of Posterior Pituitary Extract on Renal Function* *

Case No.	Experiment No.	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Effective Blood Flow, Cc./Min.	Filtration Fraction	Total Tubular Excretory Mass, I_2 (Mg.)/Min.	Diodrast Clearance/Tubular Excretory Mass	Inulin Clearance/Tubular Excretory Mass	Hematocrit Plasma Volume, %	Treatment with Solution of Posterior Pituitary, U. S. P.
			Diodrast	Inulin							
1	1	8.0	**304**	124.0	724	**0.44**	37.0	8.3	3.4	41.9	None, 7 days
	2	6.0	**381**	95.4	735	0.25		.....	.....	51.8	None, 18 days
	3	7.8	760	93.0	1,400	0.12		.....	.....	54.3	None, 4 days
	4	0.72	**737**	121.0	1,218	**0.19**	38.1	19.3	3.2	60.5†	3 daily doses, 14 days
2	5	15.0	**250**	124.0	581	**0.49**		.....	.....	43.0	None
	6	18.8	416	98.4	816	0.24		.....	.....	51.2	None
	7	18.9	444	109.0	934	0.25	50.0	8.88	2.18	47.5	None
	8	3.0	**595**	130.0	1,100	**0.22**	44.12	13.50	2.94	53.7	3 doses 2 days before and 2 doses 1 day before experiment; 1 dose on day of experiment
3	9	4.7	**382**	104.0	710	**0.27**	46.5	8.22	2.24	53.8	None
	10	3.1	480	95.3	871	0.20	.....	.....	.....	55.1	None
	11	0.55	**600**	106.3		0.18	40.24	14.9	2.64	.....	3 daily doses 4 days before experiment, 1 dose on day of experiment
	12	0.75	483	98.6	792	0.20	29.83	16.2	3.30	60.9	3 daily doses 3 days before experiment, 1 dose on day of experiment
4	13	9.8	665	109.0	1,147	0.16	41.8	15.9	2.37	58.0	None, 10 days
	14	5.0	618	143.0	1,104	0.23		.....	.....	56.0	None, 5 days
	15	1.1	639	80.0 ‡	1,070	0.13	46.8	13.6	1.71	59.7	Extract given
5	16	13.5	**585**	152.0	959	**0.26**		.....	.....	60.9	None, 2½ days
	17	7.0=15.0§	**704**	140.2	1,164	**0.20**		.....	.....	60.5	Extract given

* The plasma clearance is generally depressed, particularly when pituitary extract has not been administered for some time. The values of maximum difference are set in heavy type. The glomerular filtration rate is practically constant. The total tubular excretory mass shows only slight change.

† This reading was made independently after a week's treatment with pituitary extract.

‡ One cubic centimeter of solution of posterior pituitary was given fourteen minutes before the first period of measurement.

§ The antidiuretic effect of the pituitary extract was lost during the experiment.

with similar preparation and was from one-third to one-half his ordinary output. The glomerular filtration rate was constant. The total excretory mass showed only slight change on one occasion after treatment with pituitary extract and a greater diminution on another. There is no explanation for the latter change, and no significance can be attached to it.

CASE 4.—The effective plasma clearance during two periods of diuresis, for ten and five days, respectively, showed no depression. The glomerular filtration rate on both occasions was also normal. The diminished glomerular filtration rate following treatment with posterior pituitary extract was an acute effect of a dose given fourteen minutes before the experiment; therefore, it is not significant for purposes of this experiment. The total excretory mass, however, was measured well after the acute effect subsided and showed little change in either phase.

CASE 5.—Diuresis could be established for only two days because of the hardship entailed. Despite this, plasma clearance was still decreased by 20 per cent compared with that when the patient was taking posterior pituitary extract. Also, the higher clearance value during medication was obtained despite the progressive loss of antidiuretic effect during the course of the experiment. There was no essential change in the glomerular filtration rate. No measurement of the total excretory mass could be obtained in this case.

CASE 6.—Only limited essential data can be furnished in this case. The plasma clearance following diuresis of two days' duration was within normal range. It is worth noting that the patient's diuresis has recently been improving, with the fluid exchange decreasing from 10 to 6 liters per day. The glomerular filtration rate and the total excretory mass were within normal limits after treatment with posterior pituitary extract. It may also be worth mentioning an approximation that the total excretory mass was higher before medication with pituitary extract than after.

CASE 7 (table 5).[65]—It is to be noted that this patient, having had a total thyroidectomy some time before, was considerably myxedematous, with a basal metabolic rate of —25 per cent and weight of 203 pounds (92 Kg.). His surface area, therefore, was not a true reflection of his renal status. Nevertheless, the renal function was not significantly abnormal.

Generally speaking, therefore, the aforementioned experiments revealed a depression of varying degree in effective plasma clearance during the well established diuretic phase compared with that in the antidiuretic phase, while the glomerular filtration rate and the total excretory mass remained practically constant.

Acute Effect of Posterior Pituitary Extract on Renal Function (table 2).—Diuresis was established in all patients for at least two to three days before study. The effective plasma clearance was determined for three or four control periods and was again determined for several more periods after the administration of posterior pituitary extract, the dose varying with the size of the subject. The periods were usually

65. Since completion of this study, this case has been reported at length. (Blotner, H., and Cutler, E. C.: Total Thyroidectomy in the Treatment of Diabetes Insipidus, J. A. M. A. **116**:2739 [June 12] 1941).

TABLE 2.—*Acute Effect of Posterior Pituitary Extract on Renal Function* *

Experiment Number	Case Number; Date	Period, Min.	Urine Output, Cc./Min.	Diodrast Clearance, Cc./Min.	Inulin Clearance, Cc./Min.	Filtration Fraction	Dose of Solution of Posterior Pituitary U. S. P., Cc.	Hematocrit, Plasma Volume, %	Comment
1	1 3/19/41	(10.0	6.0	360	90.0	0.25		51.8)	B0 †
		Average for 5 periods							
		7.7	4.46	308	69.7	0.23	1.0	52.5	B2
		11.8	0.60	216	65.2	0.30		54.1	47 min. after pituitary extract given
		9.3	0.64	416	108.3	0.26			
		6.7	0.82	448	117.4	0.26			
2	2	(10.8	18.8)	520	(123.0	0.24		51.2)	B0
		Average for 3 periods		Average for 2 periods		Average for 3 periods			
	4/8/41	5.0	18.40	571	159.7	0.28	0.8		
		4.1	5.34	279	75.0	0.27		47.0	B3, drawn 19 min. after pituitary extract given
		4.8	3.42	307	100.4	0.33			
		13.9	2.95	467	121.4	0.26			
		10.6	2.84	561	137.0	0.24			
		10.3	3.29	650.	134.0	0.21			
3	3	(11.1	3.1	490	97.0	0.20		55.1)	B0
		Average for 3 periods							
	3/26/41	10.0	3.80	438	93.2	0.21	0.6	56.1	B2
		4.0	1.88	251	54.4	0.22			
		15.3	0.59	318	73.5	0.23		53.0	B4, drawn 48 min. after pituitary extract given
		10.0	0.55	488	98.1	0.20			
		10.4	0.62	579	103.8	0.18			

4	4	(10.0	5.0	600	139.0	0.23		56.0)	B0
				Average for 5 periods					
	2/28/41	6.8	5.42	600	131.0	0.22	1.0		
		3.7	1.09	800	83.5	0.08		60.0	B3, drawn 35 min. after pituitary extract given
		10.9	0.82	872	88.0	0.10			
		11.3	0.89	620	120.0	0.19			
5	5	(11.2	13.5	476	123.0	0.26		60.5)	B0
				Average for 3 periods					
	4/29/41	5.7	11.70	414	113.7	0.27	0.7	59.7	B2
		4.8	13.10	670	142.4	0.21		59.2	B3, drawn 32 min. after pituitary extract given
		8.8	1.37	300	69.0	0.23			
		9.4	3.50	651	138.0	0.21			
		6.8	2.30	443	94.0	0.21		56.5	B4, drawn 60 min. after pituitary extract given
		9.8	2.15	412	92.0	0.22			
6	7	(11.2	3.9	602	105.0	0.17		57.6)	B0
				Average for 4 periods					
	2/14/41	13.2	4.80	585			0.5		
		13.1	2.80	530	90.9	0.17	(middle	58.0	
		11.3	0.71	520	98.8	0.19	of period)		B3, drawn 37 min. after pituitary extract given
		12.8	0.55	300	75.8	0.25			
		12.5	0.92	588	117.1	0.20			

* A marked drop in plasma clearance and in the glomerular filtration rate was accompanied by a rise in the filtration fraction in most cases, indicative of constriction of the efferent arterioles, possibly extending to the afferent arterioles.

† B0 signifies a control sample of blood taken before the experiment. The letter plus a figure denotes the number of the sample taken after the experiment was begun.

shorter after the injection to enable detection of acute changes in function. Samples of blood for hematocrit readings were also taken before and after the injection.[66]

It is to be noted that there is a sharp drop in the glomerular filtration rate in all cases, a corresponding drop in plasma flow in all but case 4 and a rise in the filtration fraction in all but cases 4 and 5. The effect subsided within fifteen to twenty minutes, though antidiuresis persisted. In several cases (1, 2 and 3) it can be noted that the final value for renal plasma flow is even higher than those of the control periods. Hematocrit readings before and after the administration of posterior pituitary extract do not show consistent changes either in direction or in degree.

Relation of Renal Blood Flow and Glomerular Filtration Rate to Urine Output (table 3).—The patient studied was G. A., aged 13, in

TABLE 3.—*Relation of Renal Plasma Flow to Increasing Diuresis; Progressive Loss of the Antidiuretic Effect of Posterior Pituitary Extract* *

Case No.	Time, Min.	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Filtration Fraction
			Diodrast Clearance	Inulin Clearance	
5	16.9	7.2	608	126.1	0.21
(last dose of solution of posterior pituitary U. S. P. administered intranasally 2½ hr. before the experiment)	14.8	10.7	530	129.4	0.24
	11.0	12.7	627	128.6	0.21
	14.1	13.4	518	90.2	0.17
	11.9	15.3	582	95.0	0.16

* The plasma clearance and the glomerular filtration rate remain practically constant despite a progressive rise in the rate of urine output.

whom diuresis was normally severe. He was allowed to take his usual morning dose of posterior pituitary extract, and the experiment was begun two and a half hours later, when there was progressively increasing diuresis corresponding to the loss of antidiuretic effect. It was necessary to use a small catheter (no. 10 F). The study extended over five periods.

Despite the striking increase in urine output from 7 to 15 cc. per minute within the course of one hour, plasma flow and glomerular filtration rate remained practically constant. The somewhat depressed inulin clearance during the last two periods is not significant.

Effect of Administration of Water on Renal Blood Flow During Antidiuresis (table 4).—These experiments were continuations of the ones described in the section on "Acute Effect of Posterior Pituitary Extract on Renal Function" and were not begun until it was thought that

66. The tourniquet was not attached to the arm at the time that the blood was withdrawn.

TABLE 4.—*Effect of Administration of Water on Renal Function of Subjects Under the Influence of Posterior Pituitary Extract* *

Case No.; Date	Water Intake, Cc.	Time, Minutes: Duration of Period	Time, Minutes: Interval After Administration of Water	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.: Diodrast Clearance	Plasma Clearance, Cc./Min.: Inulin Clearance	Filtration Fraction	Hematocrit, Plasma Volume, %	Comment
3	Control			3.1	490	97	0.20	55.1	B0
3/26/41	Previous			0.55	498	98	0.20		B4, drawn before water ingested, 46 min. after pituitary extract given
	2 periods			0.62	579	104	0.18	53.0	
	1,500 cc.	26.7	5	0.60	512	86.7	0.17		
	in 15 min.	13.0	18.7	0.50	575	79.6	0.14		
		16.8	36.8	0.77	453	91.0	0.20	55.9	B5, drawn 31 min. after water ingested
		12.3	49.1	0.89	427	90.4	0.21		
		12.5	61.6	0.72	427	85.5	0.20		
		11.8	73.4	0.77	483	101.0	0.21	57.0	B6, drawn 76 min. after water ingested
4		Control		5.05	600	139	0.230	56.0	B0
2/28/41	1,800 cc.	Previous period		0.89	620	120	0.193	60.0	B3, drawn 35 min. after pituitary extract given
	in 6 min.	17.2	5	1.02	530	101.0	0.190		
		15.7 ‡	20.7	1.09	534	100.0	0.187	59.0	B4, drawn 22 min. after water ingested
		16.0	36.7	1.44	573	87.8	0.153		
		14.0	50.7	1.29	573	106.0	0.185		
		10.8	61.5	2.12	555	121.3	0.218		
		8.7	70.2	1.85	612	111.7	0.180		
		9.5	80.1	1.68	547	96.1	0.180		
7 §	1,100 cc.	Control		3.9	578	105	0.17	57.6	B0
2/14/41	in 7 min.	Previous period		0.92	588	117	0.20	58.0	B3, drawn 37 min. after pituitary extract given
		35.0	23.0	0.89	624				
		11.6	34.6	0.95	542	92.5	0.17	58.0	B4, drawn 55 min. after water ingested

* In all 3 cases a suggestive rise in renal plasma flow occurred after the administration of water. A low grade "diuretic" response is noted especially in case 4 despite an added dose of pituitary extract. The changes in the hematocrit reading are not significant.

‡ B0 signifies a control sample of blood taken before the experiment. The letter plus a figure denotes the number of the sample taken after the experiment was begun.

‡ An additional 0.5 cc. of solution of posterior pituitary U. S. P. was given in the middle of the experimental period to insure antidiuresis.

§ In this case a total thyroidectomy had been performed six years before this study.

the acute effect of the previously administered pituitary extract had subsided. During the antidiuretic phase, 1 to 1.5 liters of water was given by mouth over a short interval and an attempt made to detect changes in the renal blood flow as a reflection of hyperhydremia. Hematocrit readings were also made.

In cases 1 and 3 there was a slight rise in plasma flow in eighteen and twenty-three minutes, respectively, which promptly subsided to the initial level. In case 2 a repeated smaller dose of posterior pituitary extract was thought necessary to insure antidiuresis just after the administration of water with production of an acute effect, but after twenty-four minutes, well beyond the maximum time of altered clearances in the aforementioned experiments on the acute effect of pituitary extract, the rate of plasma flow was still somewhat elevated. A slight transient depression in glomerular filtration rate can also be noted.

TABLE 5.—*Renal Function After Thyroidectomy* *

Case No.	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Effective Blood Flow, Cc./Min.	Filtration Fraction	Hematocrit, Plasma Volume, %	Comment
		Diodrast Clearance	Inulin Clearance				
7	3.9	506	88	880	0.17	57.6	No treatment with solution of posterior pituitary

* The effective plasma clearance and the glomerular filtration rate are within normal limits.

COMMENT

The Tubule Cell as the Site of Pathologic Function in Diabetes Insipidus.—It is apparent from the data presented that glomerular filtration as measured by inulin clearance is essentially unchanged in the well established diuretic and antidiuretic phases, indicating the absence of any glomerular mechanism in the pathogenesis of diabetes insipidus, as well as the independence of glomerular filtration and urine output in general. This is in complete accord with the studies in diabetes insipidus by Schmitz [53] but not with the animal experiments of White and associates [67] if their studies may be placed on a comparable basis. The last-named authors reported a reduction in glomerular filtration as measured both by creatinine and by inulin clearance in hypophysectomized dogs.

On the basis of the studies presented here it can be reasoned that if the inulin clearance is known to be the same in both phases, the filtrable fraction of diodrast must also be the same, so that whatever variations

67. (*a*) White and Heinbecker (footnotes 54, 55 and 56*a*). (*b*) White, Heinbecker and Rolf.[56b] (*c*) Heinbecker, P.: Personal communication to the author.

do occur in effective plasma clearance must be attributed to the tubule cells. If one omits case 6, except for a few pertinent remarks later, it will be observed that in all cases other than case 4 the effective plasma clearance is persistently lower when posterior pituitary extract is not given than when it is administered. The clearance under the first-named condition may range from 20 to 60 per cent below the values obtained during medication. If one assumed that practically all the blood flowing through the kidney comes in contact with the clearing mechanism, as there is no obvious morphologic change, microscopically, that would account for a deflection of blood away from it, the depression in clearance can then be explained in one of two ways: 1. There is a decrease in the total blood volume and, hence, in the renal blood flow. 2. There is a specific impairment in the excretory function of the tubule cell.

It is agreed that the first possibility cannot be easily dismissed, since it is imaginable that during the diuretic phase there is a tendency to dehydration and actual depletion of the total blood volume, in turn reflected by decreased renal blood flow. There are several difficulties with this interpretation, however. First, previous water balance studies indicate that during the diuretic phase water intake generally parallels the output, so that the balance is at least approximately maintained.[68] Second, because the possibility of dehydration was fully realized, the patients were encouraged to drink abundantly for several days before study to compensate for diuresis. Third, in case 4 there was no decrease in the renal blood flow despite marked diuresis for two periods of five and ten days, respectively. Fourth, it is difficult to believe that the decrease in total blood volume could be so great as to account for as much as a 60 per cent decrease in renal plasma flow. Finally, the decrease in total blood volume of hypophysectomized dogs which was reported by White, Heinbecker and Rolf [56b] and which was regarded as partially responsible for diminished renal plasma flow was not measured in terms of the original weight of the animals, so that actually the total blood volume was unchanged (Heinbecker [67c]).

The alternative explanation is that the function of the tubule cell is specifically impaired by the deficiency in pituitary hormone manifested not only by the decreased power for the reabsorption of water, with subsequent diuresis, but in its reduced excretory capacity, indicated by the depression in plasma clearance. There are, ostensibly, two ways in which this might be established: 1. Given the conditions of diuresis and low plasma clearance, one should demonstrate a significant improvement in clearance following the administration of a single dose of pituitary extract. 2. During the well established diuretic and antidiuretic phases, one should demonstrate changes in the total excretory mass corresponding with changes in plasma clearance.

68. Blotner, H.: Unpublished data.

As for the first method of approach, it has been noted in table 2 that in the first 3 cases the terminal clearance values were somewhat above initial control levels after recovery from the acute effect of posterior pituitary extract. This cannot be used as evidence of improved efficiency, however, since comparable results were previously obtained by Geiling and associates,[42] Herrick,[48] Walker and co-workers[5] and Handovsky and Samaan[69] with the use of the thermostromuhr, which ostensibly measures actual blood flow. The sharp rise in case 4 appears attributable to the acute vascular effect of pituitary extract. There is no significant evidence, therefore, that a single dose of pituitary extract will promptly improve the excretory capacity of the tubule cell as it does its capacity for the reabsorption of water.

As for the second method of proof, contrary to the observations of White, Heinbecker and Rolf[56b] with reference to their hypophysectomized dogs, the total excretory mass did not show changes corresponding with those of plasma clearance. In 4 cases in which the total excretory mass was measured both in diuretic and in antidiuretic phases, the difference was slight, if any, generally not exceeding 5 to 6 mg. of iodine per minute, and not consistent in any one direction.

On the other hand, other interpretations may be sought, though here a certain degree of speculation is implied and opposition to certain accepted principles in renal function is met with. In the first instance, it may be stated that the failure of plasma clearance promptly to improve after administration of pituitary extract, is due to the fact that while the restorative capacity of the tubule cell for reabsorbing water is effective and immediate, its capacity for excretion of a solute requiring a greater amount of cell "work" is less effective and delayed. Cell recovery, therefore, requires two factors, (1) sufficient pituitary hormone and (2) sufficient time, both enabling an elevation in the degree of molecular exchange. Once this elevation is established, however, it tends to be retained despite the rapid loss of antidiuretic effect. This will explain the only slight, if any, diminution in plasma clearance in the presence of diuresis of short duration. This is best evident in case 4 and experiment 17 in case 5.

In the second instance, it may be further stated that the failure of the total excretory mass to be depressed during the diuretic phase may be due to the fact that while the tubule cell at the lower level of diodrast concentration necessary for measurement of effective plasma clearance reveals its true state of inefficiency and depressed molecular exchange, at the higher level of diodrast concentration necessary for measurement of the total excretory mass its excretory capacity increases to its normal level of function under the "driving force" of tubule cell saturation.

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69. Handovsky and Samaan (footnote 3 *b* and *c*).

Two fundamental observations, however, render this interpretation difficult. First, the concept of impaired tubular excretory function at low plasma diodrast levels apparently implies a decreased extraction ratio of diodrast by the tubule cell. White, Heinbecker and Rolf [56b] have found this to be undiminished in their hypophysectomized dogs. Second, a decreased extraction ratio at low plasma diodrast levels in the face of an undiminished total excretory mass appears contrary to the titration curve as established by Smith, Goldring and Chasis [68] and to the principle more recently stated by Smith.[70] The latter merits quotation.

> But whether the retarding factor is conceived as a positive barrier (e. g. impermeable connective tissue) or a negative fault (e. g. failure of the tubule cell to handle all molecules available to it), it would be expected that the retardation would operate on any and all molecules of diodrast with statistical indifference, with the result that the clearance probabilities for any particular molecule would not be increased by increasing the number of molecules.

As to the first point, without intending to offer the following comment as positive proof to the contrary, it is interesting to note that the tubular extraction ratio, as calculated from the tubular diodrast plasma clearance and the renal plasma flow, in experiment 1 compared with that in experiment 4 in case 1 and the ratio in experiment 5 compared with that in experiment 8 in case 2 did show a rise of 0.20 and 0.15, respectively. These cases represented 2 of the 4 most severe instances of diabetes insipidus in the series. The difficulty with offering this as positive proof for diminished tubular extraction is the failure to make the same observation in other instances, particularly in case 2, in which the urinary output was generally marked and pituitary extract not resorted to. On the other hand, even if one grants the contention that decreased plasma clearance is a reflection of actually decreased renal plasma flow, proper interpretation still appears wanting. Of the combination of factors responsible for decreased renal plasma flow proposed by White and associates,[56b] i. e. diminished cardiac output, decreased total blood volume and uniform renal vasoconstriction, the last two have since been withdrawn,[67c] leaving only the first, which, it appears, requires further confirmation. Further, the observation of a diminished total excretory mass in the presence of a normal tubular extraction as indicating the existence of a quantitatively but not qualitatively deficient hypothetic substance appears to imply an "all or none law" of tubule cell function—that at any one time a certain number of tubule cells are not functioning at all. This seems necessary, since there is no other morphologic change, such as fibrosis, to account for a diminution in the total excretory mass. It may be asked why the behavior of the tubule cells, numerically, should

70. Smith, H. W.: Note on the Interpretation of Clearance Methods in the Diseased Kidney, J. Clin. Investigation **20**:634, 1941.

be regarded as different from that of the glomeruli, all of which are believed to function at any one time.[71] Finally, one may question the comparability of function in a hypophysectomized animal with that in a human subject with diabetes insipidus, though, truly, the observations in the former should be highly suggestive.

As to the second criticism, this one cannot be easily dismissed either. It might be contended, however, that these principles apply only to the normal human kidney or the morphologically damaged kidney in which the tubule cell is under adequate hormonal control. Whether the same is true for the kidney in a person with diabetes insipidus may be questioned. Certainly, the observations of White and associates[56b] would corroborate the similarity in behavior.

It is worth noting that the concept of the posterior pituitary controlling the function of the tubule cell in a respect other than water reabsorption has recently been gathering other suggestive support. First, the evidence proposed by Silvette[72] and Silvette and Britton[73] suggested the independence of water reabsorption in relation to chloride. Second, the studies of Harrison and Darrow[74] offered direct proof of the deficiency of chloride reabsorption by the tubules in the absence of adrenal cortex hormone. This, according to the belief expressed by Silvette and Britton, lends credence to the antagonism between the pituitary and the adrenal cortex hormones occurring within the tubular epithelium.

In conclusion, from the data presented here it is difficult to consider diminished plasma diodrast clearance as absolute proof of a diminution of tubular excretory function, though there is suggestive evidence in at least 2 instances to the contrary. Certainly, if the interpretation of these observations were based solely on the diminution of total renal plasma flow, the clearances would indicate a normally functioning kidney. However, until more basis for this is obtained and the subject pursued to its more logical conclusion, some doubt will persist.

Effect of Posterior Pituitary Extract on the Glomerulus.—It has already been noted (table 1) that during the well established diuretic

71. Smith, H. W.: Studies in the Physiology of the Kidneys, in Porter Lecture Series, no. 9, Lawrence, University of Kansas, University Extension Division, 1939, p. 89.

72. Silvette, H.: The Influence of Post-Pituitary Extract on the Excretion of Water and Chlorides by the Renal Tubules, Am. J. Physiol. **128**:747, 1940.

73. Silvette, H., and Britton, S. W.: Renal Function in the Opossum and the Mechanism of Cortico-Adrenal and Posterior Pituitary Action, Am. J. Physiol. **123**:630, 1938.

74. Harrison, H. E., and Darrow, D. C.: Renal Function in Experimental Adrenal Insufficiency, J. Clin. Investigation **17**:505, 1938; Renal Function in Experimental Adrenal Insufficiency, Am. J. Physiol. **125**:631, 1939.

and antidiuretic phases the glomerular filtration rate is practically constant. As to the acute effect of pituitary extract, previous investigators,[75] applying various clearance methods other than that used by Corcoran and Page,[45] could not detect any significant change in the glomerular filtration rate. It should be stated, however, that Richards and Plant [14] and Adolf [47] early demonstrated, by other methods, that small doses of solution of posterior pituitary produced a pure constriction of the efferent arteriole, with maintenance of or rise in the glomerular filtration rate, while large doses extended this constriction to the afferent arteriole as well.

In table 2 it can be seen that in practically all cases there was a prompt significant drop both in glomerular filtration rate and in renal plasma flow, as much as 50 per cent or more, with an associated rise in filtration fraction, which gradually returned to its original level within fifteen to twenty minutes. If one bases one's reasoning on the work of Chasis, Ranges, Goldring and Smith,[7] it is fair to assume that the effect observed here after the administration of pituitary extract is due to a predominant constriction of the efferent arteriole. In view of the marked decrease in glomerular filtration rate, it is believed that this constriction may involve the afferent arteriole as well. This would be in accord with the results reported by Richards and Plant [14] when they used large doses of solution of posterior pituitary, to which the doses used here are comparable. The reason for the unique behavior in case 4 is not clear. It is concluded that pituitary extract in relatively large doses will produce a predominant constriction of the efferent arteriole and that its effect will possibly extend to the afferent arteriole.

Effect of Posterior Pituitary Extract on Renal Blood Flow.—The considerable disagreement among early workers [76] on this problem has already been noted. Later investigators [77] were more in agreement that there is a slight initial transient diminution in renal blood flow, which returns to the original level or to an even higher one. In the cases presented here, except case 4, posterior pituitary extract produced a sharp, significant drop in the renal blood flow, as much as 50 per cent or more, which returned to its original level within fifteen to twenty minutes and in the first 3 cases eventually reached a level above that of the control period. The suggestion of the supposed causal relation between renal blood flow and antidiuresis attributed to Handovsky and

75. Walker, Schmidt, Elsom and Johnston.[5] Poulsson.[23] Burgess, Harvey and Marshall.[48] Gersch.[50]

76. Richards and Plant.[14] Motzfeldt.[21] Priestley.[23] Dale.[37] King and Stoland.[38] Knowlton and Silverman.[39] Abel and Geiling.[40]

77. Handovsky and Samaan.[69] Walker, Schmidt, Elsom and Johnston.[5] Brings and Molitor.[41] Geiling, Herriek and Essex.[42] Herrick.[43] Corcoran and Page.[45]

Samaan,[69] by Walker and associates,[5] and explained by the last-named authors as due to the intravenous route of administration of pituitary extract does not appear to be a valid argument, since the injections in the study reported here were all given subcutaneously, yet the drop in renal blood flow was sharp. As for the relation of renal blood flow to antidiuresis, it is obvious that this is not a factor, since antidiuresis persists despite the eventually raised rate of renal blood flow.

It is worth noting that in case 7 as in the other cases, despite thyroidectomy, the acute effect of posterior pituitary extract was much the same in relation both to the glomerular filtration rate and to the renal blood flow except for a moderate prolongation of the latent period till maximum response was obtained. This slowed response may be due to the combined effect of the presence of myxedema, hence slower absorption, and the smaller dose (0.5 cc.) of extract used. It appears, therefore, that the absence of the thyroid does not alter the acute action of pituitary extract and that the effective plasma clearance is within normal range.

Relationship of Renal Plasma Flow and Glomerular Filtration to Urine Output.—Case 5 offered the opportunity of studying the relation of renal blood flow and glomerular filtration to urine output from a slightly different standpoint from that used by other investigators. Chasis, Ranges, Goldring and Smith[7] and other authors previously studied this relation by administering water to a subject and noting the state of these two factors during the resulting period of water diuresis. In the study presented here, the conditions were reversed. The patient was initially under the antidiuretic control of pituitary extract, which was allowed to diminish with progressively increasing diuresis until the initial volume of urine was more than doubled during the course of the experiment (table 3). This approach offered the advantage of avoiding any extrinsic factors associated with the oral administration of a large amount of fluid. It is noteworthy that despite the markedly increasing diuresis, the renal plasma flow and the glomerular filtration rate were practically constant throughout. This offers further confirmation that renal blood flow and glomerular filtration, on the one hand, and urine output, on the other, are entirely independent of one another. By deduction, one may infer that water excretion must be dependent solely on the state of tubular reabsorption.

Relation of Renal Blood Flow to the Administration of Water During Antidiuresis.—It was originally thought possible to make distinctive observations on (1) the production of an accentuated hydremia following water administration, as manifested by changes in the renal blood flow, while the subject was under the antidiuretic influence of posterior pituitary extract; (2) the presence of a diuretic response to water under

antidiuretic conditions, and (3) the demonstration of a relation between the peak of the water load and the diuretic response.

In the past many different methods have been used, but most consistent results have been recently obtained by means of gravimetric estimation of total solids and changes in electrical conductivity of serum. These have been reviewed at some length by Findley and White.[78] The consensus of later opinion favored a slight transient hyperhydremia, with a latent period between the peak of the water load and the diuretic response. Since then, Handovsky and Samaan,[69] studying renal blood flow by means of the thermostromuhr, detected a rise after the administration of water and actually attributed diuresis to the stimulus of hyperhydremia. Chasis, Ranges, Goldring and Smith,[7] using diodrast clearance in normal human subjects, could not detect any rise in renal plasma flow related to water diuresis.

The result of the studies undertaken here have proved disappointing. In 3 cases a slight transient rise occurred in the renal plasma flow, but it was not sufficient to be more than suggestive. Similarly, no conclusions can be safely drawn on the relation of the peak of the water load to the diuretic response.

As for the diuretic response, the impression gained is that a low grade "diuretic" curve occurs within fifty to sixty minutes, best demonstrated in case 2, in which it may also be pointed out that the repeated dose of pituitary extract did not produce further depression in the urine output or affect the shape of the curve. In case 3 the complete curve is not noted, but here, too, there was a low grade diuretic response. In conclusion, then, the studies presented only suggest that after administration of water to a person under the antidiuretic influence of pituitary extract, a transient hyperhydremia is followed by a low grade "diuretic" response.

Hematocrit Reading in Relation to Posterior Pituitary Extract.—It was thought that during study of the acute effect of pituitary extract on renal function, with or without the administration of water, characteristic changes in the hematocrit reading might be detected. Previously Underhill and Pack [27] and Craig [26] noted a definite reduction in the percentage of hemoglobin in the blood of dogs after the administration of solution of posterior pituitary without and with administration of water. The observations cited in table 4 did not prove as definite. The highly encouraging result obtained in the first case studied (case 4, table 2), a rise of 4 per cent in the plasma volume in thirty-seven minutes after the injection of pituitary extract, was not borne out in the other cases. Thus, in cases 1

78. Findley, T., Jr., and White, H. L.: Response of Normal Individuals and Patients with Diabetes Insipidus to the Ingestion of Water, J. Clin. Investigation **16**:197, 1937.

and 6 the rise was slight but not significant, while in cases 2, 3 and 5 there was a fall up to 4 per cent (table 2). Even in those cases in which water was administered while the subject was under the influence of pituitary extract (table 4), there was no significant change, except in case 1, in which instance it must be realized that the rise occurred from the lowest depressed point following the injection of pituitary extract. As for the hematocrit reading during the well established diuretic and antidiuretic phases (table 1), it may appear that in a general way, the highest percentage of plasma volume accompanies the highest plasma clearance and vice versa. Careful scrutiny, however, will reveal instances in which the hematocrit difference is slight with a disproportionate difference in clearance or is significant with no difference in plasma clearance. No conclusions, therefore, can be drawn from the foregoing observations on the relation of pituitary extract to the hematocrit reading.

SUMMARY AND CONCLUSIONS

The renal function in 7 cases of diabetes insipidus (in 1 case total thyroidectomy had been performed) was studied by means of inulin and diodrast clearances with the intention of establishing the site of pathologic change in terms of function.

The comparison of function during the well established diuretic phase with that during the antidiuretic phase revealed a decrease in effective plasma clearance in the diuretic phase, in most instances from 20 to 60 per cent below clearance during the antidiuretic phase. This did not tend to be true if the diuresis was of short duration. The glomerular filtration rate and the total excretory mass (T_m) were relatively constant in both phases. It might be suggested that the decrease in plasma clearance is due to an impairment in the excretory function of the tubule cell which is restored under the influence of repeated administration of solution of posterior pituitary. Also, the constancy of the total excretory mass during the diuretic phase might be explained by the elevation of functional level under the "drive" of tubule cell saturation. However, absolute proof of this cannot be offered from the data obtained. Besides, data from other studies controvert this interpretation. That decreased total blood volume may cause decreased clearance is not altogether ruled out, though it is not felt to be the responsible factor.

The administration of solution of posterior pituitary, producing an acute transition from diuretic to antidiuretic phase, was accompanied by a sharp drop in the glomerular filtration rate and in the renal plasma flow, with a rise in the filtration fraction. The acute effect subsided within fifteen to twenty minutes, with the plasma flow in 3 of 5 cases eventually reaching a level above that of the control period. The effect

is believed due to a predominant constriction of the efferent arterioles, possibly extending to the afferent arterioles.

The study of the relation of renal plasma flow and glomerular filtration to urine output during the course of progressively increasing diuresis with corresponding loss of the antidiuretic effect of posterior pituitary extract revealed their independence of one another. This offers corroboration for the hypothesis that excretion of water is a function of tubular reabsorption.

Suggestive evidence is presented for the occurrence of a transient hyperhydremia and a low grade "diuretic" response following the administration of water to a subject under the antidiuretic influence of posterior pituitary extract.

There appears to be no consistent change in the hematocrit reading following administration of solution of posterior pituitary with or without the administration of water.

Dr. Harry Blotner cooperated in securing the case material studied and permitted me to make use of his clinical records; Drs. Soma Weiss, James P. O'Hare, G. Philip Grabfield and Allen M. Butler contributed suggestions; Drs. Homer W. Smith, James A. Shannon and Alf S. Alving gave counsel in questions of technic, and Miss Betty Eichorn gave technical assistance.

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

WITHOUT CUTANEOUS MANIFESTATIONS AND WITH HERETOFORE UNDESCRIBED PULMONARY LESIONS

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As more and more observations are recorded on the clinical syndromes of acute disseminated lupus erythematosus and atypical verrucous endocarditis, it becomes more apparent that they constitute slightly varying but confusing manifestations of the same disease. These observations include the erythema group of cutaneous diseases with visceral manifestations first clearly pointed out by Osler [1] in 1904; the atypical verrucous endocarditis recognized by Libman in 1911 and reported more fully by Libman and Sacks [2] in 1924; the polyserositis, polyarthritis and glomerulonephritis with long-continued fever described by Christian [3]; a diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis, reported by Baehr and associates [4] in 1935; the nonbacterial thrombotic endocarditis accompanied by prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions described by Friedberg, Gross and Wallach [5] in 1936, and the generalized capillary and arteriolar thrombosis described by

From the Kingston Hospital (Dr. Rakov) and the City of Kingston Laboratories (Dr. Taylor).

1. Osler, W.: On the Visceral Manifestations of the Erythema Group of Skin Diseases, Am. J. M. Sc. **127**:1 (Jan.) 1904.

2. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701 (June) 1924.

3. Christian, H. A.: Long Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis: A Clinical Syndrome of Unknown Etiology, M. Clin. North America **18**:1023 (Jan.) 1935.

4. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), Tr. A. Am. Physicians **50**:139, 1935.

5. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med. **58**:662 (Oct.) 1936.

Gitlow and Goldmark [6] in 1939. The Reifensteins [7] have pointed out this relation in a convincing manner; Osler long before them stated that while a great number of the erythemas, including simple erythema, erythema exudativum, herpes iris, erythema nodosum, certain of the purpuras, urticaria and angioneurotic edema, are usually described as separate diseases, they belong to one family, and he characterized them as follows:

> . . . by the similarity of the conditions under which they occur, the frequency with which the lesions are substituted the one for the other in the same patient at different times, the tendency to recurrence, often through a long period of years, and lastly, the identity of the visceral manifestations.

It is fairly clear that a diffuse vascular process involving the smaller blood vessels of the skin and the viscera is the essential lesion of these signs and symptoms. Because in all of these clinical syndromes cutaneous lesions at some time are erythematous and widespread, they are now classified as lupus erythematosus disseminatus. This disease most frequently suggests itself to the observer because of the very complexity of its manifestations. At times it simulates acute rheumatic fever, subacute bacterial endocarditis and polyserositis with subacute glomerulonephritis, yet never quite fulfils the diagnostic criteria of any one of these disorders. The prolonged fever, polyarthritis, polyserositis, evidence of endocarditis and tendency toward remissions frequently lead to the diagnosis of the rheumatic state. Endocarditis, erythematous cutaneous nodules, nephritis and anemia, especially when white-centered petechiae appear, point strongly to the diagnosis of endocarditis lenta. The long-continued fever with conspicuous involvement of the serous cavities and synovial membranes and the eventual glomerulonephritis without signs of endocarditis may lead to a diagnosis of subacute Pick's disease.[8]

But to one who observes the condition from day to day the persistent leukocytopenia, cutaneous rash, white-centered petechiae and nephritis make the diagnosis of rheumatic fever untenable. Likewise the presence

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6. Gitlow, S., and Goldmark, C.: Generalized Capillary and Arteriolar Thrombosis: Report of Two Cases with a Discussion of the Literature, Ann. Int. Med. **13**:1046 (Dec.) 1939.

7. Reifenstein, E.; Reifenstein, E., Jr., and Reifenstein, G.: A Variable Symptom Complex of Undetermined Etiology with Fatal Termination (Including Conditions Described as Visceral Erythema Group (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian) and Diffuse Peripheral Vascular Disease (Baehr and Others), Arch. Int. Med. **63**:553 (March) 1939.

8. Tremaine, M. J.: Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis, New England J. Med. **211**:754 (Oct. 25) 1934.

of acute pericarditis and polyserositis with blood cultures persistently negative for growth and the presence of leukocytopenia are incompatible with the diagnosis of subacute bacterial endocarditis. The cutaneous rash, polyarthritis, leukocytopenia and nephritis rule out Pick's classic pericarditic pseudocirrhosis of the liver, but because of the prominent adhesive pericarditis and polyserositis the syndrome has been classified as subacute Pick's disease with polyarthritis and glomerulonephritis. And so we might continue with the remainder of these protean syndromes of unknown origin bearing close resemblance to many infectious diseases and encumbered with lengthy titles which only add confusion to the nomenclature and diagnosis. A careful analysis of the clinical and pathologic data seems to indicate that all are intimately related and that the essential lesion is endotheliitis almost always accompanied by polymorphous cutaneous lesions.

The possibility that acute disseminated lupus erythematosus may appear and run its fatal course without cutaneous manifestations has frequently been mentioned, but no authenticated cases have been reported in which the cutaneous lesions did not appear at some time. Moreover, only rarely has an observer appreciated that pulmonary parenchymal lesions are specifically a part of the visceral manifestations of this disease. The clinical signs are those of long-standing consolidation, and this must be distinctly differentiated from the almost universal terminal pyogenic infection of the lungs. A proper evaluation of these pulmonary lesions seems to have been made by Osler [1] (case 26) and later by Tremaine [8] (case 2). Osler stated:

> On December 27 [the patient] . . . had a chill and on the third day consolidation of the left lower lobe was found. Then the other lung became involved [26th day]. . . . The right lung has been clearing [3 weeks later]. The left lower lobe has been solid for some weeks. I put a needle in two places, but got nothing.

Tremaine reported:

> Throughout the four months [the patient] . . . remained in the hospital there were frequent bouts of fever, chills and joint pains. The physical signs of a small amount of fluid at the bases of both lungs, and of consolidation at the inferior angle of the left scapula were usually present. A right thoracentesis yielded 75 cc. of fluid but no organisms.

We feel that a case of acute disseminated lupus erythematosus in which we observed the patient through a long clinical course without her exhibiting at any time a characteristic rash, a unique circumstance, should be reported. Furthermore, the long-continued consolidation of the lungs leads us to believe that the pulmonary parenchymal changes are an integral part of the disease, comparable to those encountered in the other viscera.

REPORT OF A CASE

F. N., a 24 year old white woman, whose mother died when 34 years old of rheumatic heart disease, had been healthy until Dec. 10, 1939, when she noted arthralgia and numbness of her extremities. Three weeks later a physician prescribed salicylates, but the symptoms continued unabated, yet she was able to carry on her work as an examiner in a pajama factory. On Jan. 8, 1940 she experienced severe pain over the precordium extending into the left axilla, after which she became thirsty and drank increasing amounts of water. Nervousness, insomnia, asthenia and dyspnea followed in rapid succession, and she lost some weight but had no cough and experienced no night sweats. She was first seen by one of us (H. L. R.) on January 29, and because of signs of consolidation at the base of the left lung, hospitalization was advised.

On admission to the Kingston Hospital, the patient was not acutely ill, the temperature was 101.2 F., the pulse was 140 per minute and regular, the respirations were 32 per minute but not labored and the blood pressure was 84 systolic and 60 to 58 diastolic, measured in millimeters of mercury. Signs of consolidation at the base of the left lung, confirmed roentgenologically, were present. There were 5,600 white cells per cubic millimeter of blood and severe secondary anemia. The urinary sediment contained a few pus cells and a rare erythrocyte. The scanty sputum contained no acid-fast bacilli, but pneumococci of types XIX, XX and XXIV were present. Blood cultures yielded no growth after nine days' incubation.

After two days' administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) the concentration of the free drug in the blood was 5.5 mg. per hundred cubic centimeters, but to our astonishment the patient's condition grew worse rapidly. On February 3, the temperature had risen to 104.8 F., the pulse rate was 160 and the respiratory rate was 40 per minute, and she was placed in an oxygen tent. A thoracentesis on the left side yielded a small amount of serosanguineous fluid, from which no organisms could be isolated.

An electrocardiogram revealed low voltage with a slightly elevated ST junction in lead I, and the ascending limb of the ST segment was concave. Sinus tachycardia was evident, but there were no changes of significance in the remaining leads. These observations suggested acute pericarditis. Physical signs of pericarditis were noted after forty-eight hours, together with an inconstant slight mitral systolic murmur, and although the temperature had subsided to 101.2 F., the tachycardia and tachypnea persisted; no signs of congestive heart failure appeared.

On February 8 the murmur and the signs of pericarditis had disappeared, but evidence of consolidation at the base of the right lung was present for the first time and the temperature again rose to 104.8 F. There was change in the area of consolidation in the left lung, with numerous crepitant rales audible in the area radiating from the precordium to the left axilla. In view of the fact that adequate sulfapyridine therapy accompanied by repeated transfusions of blood failed to produce a clinical response over a period of ten days, the chemotherapy was stopped. The persistent leukocytopenia with the high fever and signs of pneumonitis and pericarditis seemed paradoxic. It was felt at this time that the following observations pointed to the diagnosis of acute disseminated lupus erythematosus in spite of the fact that there were no cutaneous manifestations: arthralgia, pleuritis, pericarditis, pneumonitis, leukocytopenia with high fever, sterile blood cultures and total absence of favorable response to adequate therapy for pneumococcic infection.

A remittant fever persisted, and the temperature reached its peak of 105.4 F. on February 14, then gradually subsided to 99 F. on February 20. The patient's condition improved, and on February 22 she was removed from the oxygen tent. Not only did the signs of consolidation persist in the bases of the lungs, but the temperature rose during the next few days to 103 F. and remained elevated for another week, after which it fluctuated between 99 and 100.2 F. until March 6, when it returned to normal. At no time was splenomegaly present, and petechiae were never observed. The blood pressure persisted at a low level. Repeated blood cultures were negative for growth. Examination of the urine always revealed a few blood cells, many pus cells and albumin, yet there was never any nitrogen retention in the blood. The erythrocyte sedimentation rate was persistently accelerated; the thrombocytes remained at a normal level, and serologic reactions for syphilis were negative.

On discharge from the hospital on April 19, the respiratory rate was normal, but the tachycardia and signs of consolidation of the lungs were still present. An electrocardiogram made at this time showed low voltage and an isoelectric T wave in lead I and inverted T waves in leads II, III and IV-F, which was considered indicative of chronic adhesive pericarditis. The signs of persistent consolidation at the bases of both lungs were erroneously considered to be Ewart's sign in spite of bilateral involvement and our failure to demonstrate physical and roentgenologic signs of massive pericardial effusion. That these signs were the result of pneumonia seemed unlikely; instead they were thought to be evidence of persistent pulmonary atelectasis, resulting from earlier pericardial effusion. Carbon dioxide inhalations had not effected an expansion. The final diagnosis on discharge rested between rheumatic fever with pericarditis and acute disseminated lupus erythematosus.

For five months after her discharge the patient was afebrile. However, in spite of constant rest in bed the pulse rate remained rapid; she failed to gain weight, remained asthenic and was slightly dyspneic. During this interval, the signs of consolidation at the bases of the lungs persisted, but there was no cough, and no murmurs or adventitious sounds were heard on auscultation over the precordium. The rate of erythrocyte sedimentation continued rapid. Electrocardiograms revealed inversion of the T wave in all four leads but no prolongation of the PR interval. Mantoux and patch tests for tuberculosis gave negative results. The urine contained a few pus cells in the sediment. Roentgenograms of the chest made on June 3 showed the cardiac silhouette to be of normal size with obliteration of the costophrenic angles by shadows of increased density indicative of pleural involvement, and above this the pulmonary fields appeared clear except for a slight thickening of the lung root. Mild secondary anemia persisted but at no time was there leukocytosis. No cutaneous manifestations appeared even after prolonged exposure to sunlight.

Early in September 1940, after an episode of pharyngitis, the patient again became febrile and dyspneic. On her second admission to the hospital, September 18, the temperature was 103.2 F., the pulse rate was 130 per minute and regular and the respiratory rate was 38 per minute. There was slight cyanosis of the finger tips and the lips, with beginning clubbing of the fingers. Her dyspnea was only slightly relieved by oxygen. The white cell count was now 3,700 per cubic millimeter of blood, with 80 per cent polymorphonuclears, and the sedimentation rate of erythrocytes was still rapid. The electrocardiogram now showed low voltage in lead I with a slightly elevated concave ST segment, upright T waves in leads II and IV and an inverted T wave only in lead III. This was regarded as evidence of superimposition of the pattern of acute peri-

carditis on a previous pattern of chronic adhesive pericarditis. Repeated blood cultures remained sterile after fourteen days' incubation. Again red blood cells, pus cells and albumin were found in the urine, but there was no elevation of the blood nonprotein nitrogen. The blood pressure was 86 systolic and 60 diastolic. The cardiac shadow was slightly larger than on previous roentgen examinations; the pulmonary conus was more prominent; the left costophrenic angle was obliterated, and the infiltration of the right lower bronchial tree was increased, but far less than the tubular breathing and the egophony at the areas in the bases of the lungs led one to believe. On auscultation over the precordium only a gallop rhythm was noted. Splenomegaly and lymphadenopathy were not observed. The patient's condition became progressively more grave, with the temperature fluctuating between 102 and 104.4 F., until her death on September 30.

The final diagnosis lay between the rheumatic state and lupus erythematosus disseminatus. We felt that the rheumatic state was the more likely condition.

Necropsy.—The skin of the body was tanned over the exposed parts; elsewhere it was white. The ankles and the dorsum of each foot seemed a little swollen, but there was no edema of the pitting variety. In the abdominal cavity there was a small amount of free fluid. A moderately enlarged spleen was bound to the abdominal wall and the under surface of the left lobe of the liver by extensive, friable adhesions. Likewise the liver, which was not enlarged, was covered by adhesions, similar to those over the spleen. The stomach and the intestines showed nothing striking. The liver markings were distinct, the tissue was dark, and a few small yellow areas were present. The enlarged spleen was four times its normal size and had conspicuous malpighian bodies and a pulp which was firm. It in no way resembled the spleen of hemolytic jaundice or of bacterial endocarditis. The kidneys showed no abnormalities other than a few definite petechial hemorrhages in the cortex. The pelvic organs were not remarkable, and only a small corpus luteum of menstruation was present in one ovary.

The most extensive, and perhaps most significant, changes were found in the thoracic cavity, where the entire pleural spaces were obliterated by easily separated adhesions like those over the spleen and liver. The lungs were small and atelectatic. Particularly was this true of the lower lobes which no longer extended into the costophrenic angles of the pleural cavities but were rigidly held in an atelectatic state high on the diaphragm by the adhesions just described. These adhesions were not edematous. A careful exploration of the major bronchi and their minor branches failed to reveal an obstruction or anything else which could account for the atelectasis. After the lungs were removed and sectioned the lower lobes were observed to be collapsed; the tissue was firm and practically airless, but the gross appearance was not quite that seen in organizing pneumonia. The remaining lobes were air containing and showed no gross evidence of tuberculosis, atelectasis or organizing pneumonia. The peribronchial lymph nodes were a little large, were firm and lay in somewhat fibrous mediastinal tissue.

The pericardial sac as observed from the outside was enlarged, suggesting that it contained a large heart, but when an attempt was made to open the pericardial sac there were found extensive, friable adhesions between the pericardium and the epicardium, which accounted readily for the enlargement of the pericardial sac. In places these adhesions were many millimeters thick, and everywhere they bound the pericardial and the epicardial surfaces together, obliterating entirely the pericardial cavity. After the heart was separated from these adhesions, it was obvious that it was not enlarged. Small grayish and translucent nodules were seen along the course of the small blood vessels in the epicardium. On

opening the cavities of the heart it became clear that the right auricle was small, that the tricuspid valve was delicate and normal and that the right ventricle showed nothing unusual, which was also true of the pulmonary conus and the valve leaflets. Likewise the left auricle with its appendage was rather small. The mitral valve, on the other hand, showed along its line of closure a few granular vegetations, all of which had smooth glistening surfaces. In one or two places these vegetations were reddened, but they had not the appearance of bacterial endocarditis. The aortic valve showed perhaps the most interesting and significant lesion found in the heart. In the endocardium covering the sinus aspect of the anterior leaflet there was a flat, spreading, granular vegetation with sharply outlined edges and a reddish color, extending over 3 to 4 mm. of the central portion of the valve surface. It did not extend to involve the filmy edge. In the anterior cusp, underlying the corpus arantii, was a thickening which was slightly yellowish, a change which is commonly found in these leaflets. Flat mural endocardial vegetations were not observed, nor were pocket lesions present. The myocardium, even though a little pale, was not the seat of any gross scarring and showed only a few distinct thick-walled blood vessels. The major coronary arteries were unobstructed. The aorta was free from arteriosclerotic change. The superior and inferior venae cavae were entirely normal in appearance.

The bony framework showed nothing more than a slight clubbing of the fingers.

Restrictions on the extent of the examination prohibited a study of the brain.

Histologic Examination.—The changes in the lungs are difficult to describe, but it is clear that they have been present for a long time. In the more consolidated areas it is almost impossible to say how the consolidation developed, i. e., whether the inflammatory cells first appeared in the interalveolar tissue and eventually encroached on the alveoli and collapsed them or whether the alveoli were the seat of the early changes. As the lung is observed in its present state there is a lobular consolidation, and the intervening air-containing alveoli are surrounded by thickened alveolar septums in which there is a low grade chronic inflammation. The inflammatory cells are almost universally of the mononuclear type; some are doubtless lymphocytes; a few are plasma cells, but the most characteristic, and, of course, most conspicuous, cell is a large mononuclear containing a deeply stained nucleus usually somewhat eccentrically placed and surrounded by a wide zone of slightly pinkish-staining cytoplasm (fig. 1). As the more consolidated areas are approached, this inflammatory reaction becomes more extensive and brings about a collapse of the alveoli. In these more affected areas, alveolar walls have disappeared and the lung tissue appears as a solid inflammatory mass in which the normal structural detail is completely lost, but in which the larger blood vessels are still identifiable. In some areas, in which the destruction is not so far advanced, hyaline plugs occur in the compressed alveoli. There are alveoli in which some polymorphonuclear leukocytes are embedded in a fibrin network which looks like a fresher pneumonia and is perhaps terminal. It is evident that this is not the ordinary type of organizing pneumonia with replacement of the collapsed lung by scar tissue. The greatly thickened pleural aspect of the lung is made up of a fibrous tissue which is highly vascular and still the seat of a fairly intense inflammation consisting almost entirely of mononuclear elements. A similar thickening and inflammation is present in the interlobar fissures.

In a section so prepared that a piece of lung and of pericardial wall is shown it becomes clear that the thickened pleural adhesions are much older and less intensely inflamed than those of the pericardium. The evidence for this is the

compact fibrous tissue with far fewer vascular channels in the pleural than in the pericardial adhesions. Likewise, the blood vessels in the thickened pleura have prominent walls and flattened endothelium, while those in the pericardial adhesions have delicate walls and prominent endothelium and their supporting stroma is more loosely arranged. In the pericardial adhesions there are also small foci of necrosis and hemorrhage. As one passes to another section showing the epicardium, it is observed that the adhesions over this surface are similar to those already described in the pericardium, that the mononuclear inflammatory reaction extends down to the myocardium and that in a few places mononuclear cells can be seen in the depth of the myocardium. They are usually confined to the perivascular tissue, but an exhaustive search fails to reveal a lesion or any cells which in the slightest manner resemble Aschoff bodies. In an occasional vessel there is a hyaline thrombus; this is apparently associated with some

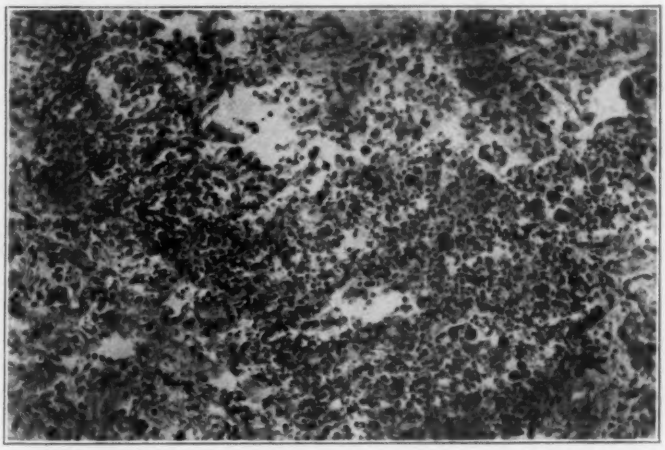

Fig. 1.—Inflammatory changes in the periphery of the lung adjacent to the pericardium.

necrosis of the vessel wall, but the change is certainly not that of periarteritis nodosa.[9] The myocardium itself seems well preserved; the muscular bundles and fibers are not hypertrophied, and no significant scarring is demonstrable.

The lesion on the sinus aspect of the aortic leaflet consists of an avascular thickening with a superficial infiltration of monocytes; near the midportion of this area is a small hyaline thrombus. At the edges of the thrombus the flattened endocardial lining seems to extend up onto the thrombus and then to become lost. One cannot be certain, but it rather appears that the endothelium originally covered this vegetation. There are no Aschoff bodies beneath the vegetation, and certainly there is none in the valve (fig. 2).

The gross lesions on the mitral valve when studied microscopically show little more than fibrous changes in which a few scattered mononuclear cells remain. There is no evidence of recent thrombi.

9. Taylor, J. S., and Farley, D. L.: Periarteritis Nodosa: A Case Report with Necropsy, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**:15 (May) 1934.

In the liver there is a rather interesting distribution of fat-laden cells. At first it appears that the zone of cells surrounding the lobule and laden with fat are the periportal cells, but on careful observation it becomes clear that a narrow zone of liver cells is well preserved immediately around the portal area. And it is between this zone of cells and the central portion of the lobule that the deposition of fat has occurred. In no place could it be seen that the fat-laden cells have as yet become necrotic.

In the kidneys, the glomeruli appear large, the loops are not distinct and there is considerable intercapillary proliferation. At frequent intervals there are seen foci of necrosis in the glomerular tufts, which in not one single instance involve

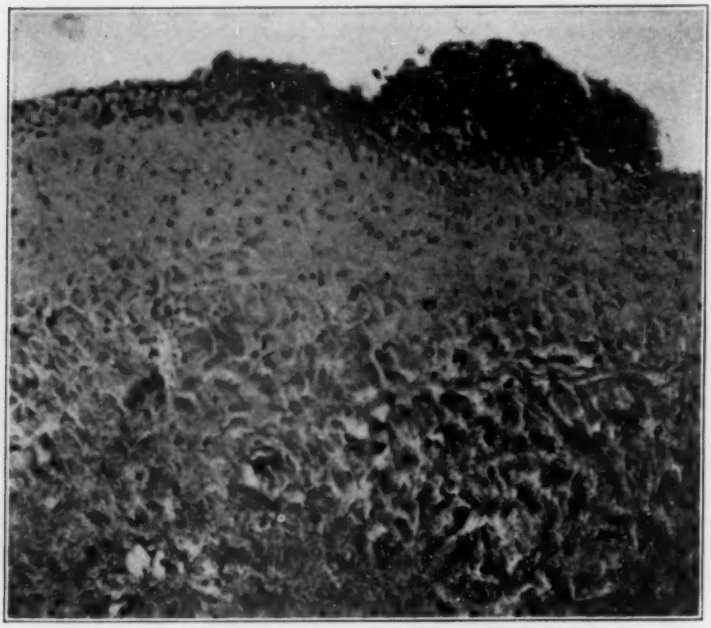

Fig. 2.—Vegetation on the aortic valve.

the entire glomerulus. Where the necrosis is not so far advanced, it appears that the vessel in the area is plugged by a hyaline thrombus. In the area of more advanced necrosis the nuclear material is broken up into small fragments, which still take a blue stain, and there are pinkish-staining colloid droplets. These necrotic zones seem clearly confined to individual loops of the capillary tuft, and in a few instances it seems that not even the entire loop is necrotic. Occasionally some portion of the glomerular tuft is adherent to the capsule, even in those glomeruli in which necrosis in the tuft is not demonstrable. Just outside of a few glomerular capsules are collections of mononuclear cells, some of which are fairly large and have an abundance of cytoplasm and a nuclear structure which resembles that of plasma cells. This inflammatory reaction is quite like that observed in the epicardium and many places in the lungs. The most

constant and striking observation in the kidneys is this mononuclear cell infiltration of the parenchyma just outside the glomerular capsule adjacent to the necrotic lesion in the tuft. There are no polymorphonuclear leukocytes, and in fact, little or no inflammation is present in these necrotic areas (fig. 3).

The spleen shows only prominent malpighian bodies and moderately thickened arterioles. In the pulp there are increased numbers of the large mononuclear cells characteristic of chronic splenic tumor.

The pancreas seems normal, as do the adrenals.

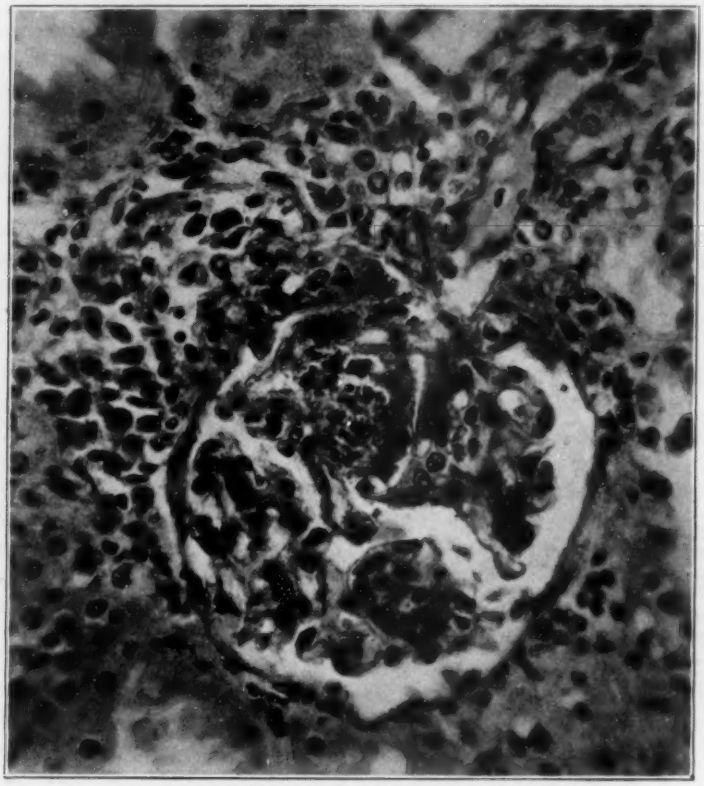

Fig. 3.—A necrotic lesion in a loop of a glomerular tuft, with accumulation of mononuclear cells in adjacent renal parenchyma outside of Bowman's capsule.

COMMENT

The clinical aspects of this case presented many symptoms and signs universally described in acute lupus erythematosus disseminatus, including prolonged fever, arthralgia, pleuritis, pericarditis, transient renal damage, leukocytopenia and persistently sterile blood cultures in a female

in the third decade of life. Thrombopenia and cutaneous lesions, including petechiae and purpura, were absent. An early presumptive diagnosis of acute lupus erythematosus disseminatus with atypical verrucous endocarditis was made, yet it was felt that the endocarditis per se did not contribute significantly to the clinical picture. The persistent signs of consolidation of the lungs were the most prominent and indeed most perplexing feature of the clinical course. These signs persisted from early in the course of the disease until death eight months later.

The accepted clinical picture of acute disseminated lupus erythematosus is usually accompanied by cutaneous lesions, which are not to be confused with the benign discoid butterfly eruption over the bridge of the nose and the malar prominences. It should be recalled that the rash of disseminated lupus erythematosus begins on the bridge of the nose as an impalpable reddish patch and may simulate for a short time the early stage of the local butterfly lesion. Before long this eruption becomes polymorphous and spreads over the face and ears and then to the skin of the neck, arms and thorax and indeed may be observed on practically any site of the cutaneous surface. On the other hand, Libman [10] has stated that the disease might occur without a cutaneous eruption and that the patient might have the general clinical picture of the disease for many months, with the eruption developing only a short time before death. Also, Baehr and associates, in reporting 23 cases of disseminated lupus erythematosus in which autopsy was done, mentioned that a similar clinical picture and somewhat similar vascular lesions in the kidneys and other viscera were observed in patients without cutaneous lesions. Yet, Rose and Pillsbury [11] expressed the belief that until the disease can be reproduced experimentally or until its cause is known, it seems unlikely that the existence of such a noneruptive form can be translated from a hypothesis into a fact. They believe, however, that the possibility of such an entity should be considered in a patient in whom no rash appears when fever, leukocytopenia, petechiae, purpura, embolic phenomena, arthralgia, evidence of endocarditis, pericarditis, renal injury, pleural effusion and persistently sterile blood cultures constitute the clinical picture. Still, with the present knowledge of acute disseminated lupus erythematosus the diagnosis is largely dependent on the presence of cutaneous lesions. And so, in the absence of cutaneous lesions a diagnosis of lupus erythematosus disseminatus is difficult to establish, even though most of the other signs of the disease are present.

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10. Libman, E.: The Varieties of Endocarditis and Their Clinical Significance, Tr. A. Am. Physicians **53**:345, 1938.

11. Rose, E., and Pillsbury, D.: Acute Disseminated Lupus Erythematosus: A Systemic Disease, Ann. Int. Med. **12**:951 (Jan.) 1939.

Just as it is difficult to establish the diagnosis on clinical grounds, so, too, is it difficult to make the diagnosis on postmortem examination. At necropsy the cutaneous lesion is the most constant single gross observation, but often fibrinous pericarditis, atypical verrucous endocarditis and polyserositis are also encountered. Histologically there may be evidence of diffuse endotheliitis described by Baehr and associates as (1) simple dilatation of capillary beds in certain areas, as in the skin, with extravasations of blood and serous fluid; (2) proliferative lesions of the endothelial lining of capillaries, arterioles and venules associated with thrombi which often occlude the lumen, and (3) degenerative and necrotizing lesions of the walls of such vessels with thrombosis and sometimes hemorrhage into the adjacent tissues. They expressed the opinion that the peculiar hyaline thickening of the capillary walls of the glomerular tufts, the so-called "wire loop lesion," is almost pathognomonic of acute disseminated lupus erythematosus. Others expressed the belief that this common distinct renal lesion does not exist (Stickney and Keith [12]), and it is true that in many fatal cases the patients do not show it (Mallory [13]). Atypical verrucous endocarditis now considered a part of this syndrome has been adequately described by Libman and Sacks, and later by Gross,[14] and in equivocal cases the endocardial lesion can be differentiated from rheumatic endocarditis by absence of Aschoff bodies in the myocardium. Curiously enough, in these cases in which there is endocardial and pericardial involvement the myocardium is usually spared, and cardiac hypertrophy is rare. Yet in many cases the heart is entirely free from any endocardial involvement. Clearcut pulmonary lesions have not been described. Indeed, we are compelled to conclude that there is no single pathognomonic visceral lesion, and in doubtful cases the diagnosis seems tenable only by coordination of the clinical and the pathologic aspects.

Our patient exhibited many of the critical manifestations of lupus erythematosus disseminatus, namely, prolonged clinical course with fever, sterile blood cultures, leukocytopenia, endocarditis, arthralgia, adhesive pericarditis with polyserositis and glomerular lesions. In addition, there were noted long-continued signs of consolidation in the lungs caused by the pulmonary changes already described. The glomerular

12. Stickney, J. M., and Keith, N. M.: Renal Involvement in Disseminated Lupus Erythematosus, Arch. Int. Med. **66**:643 (Sept.) 1940.

13. Acute Disseminated Lupus Erythematosus, Cabot Case 24201, New England J. Med. **218**:838 (May 19) 1938.

14. Gross, L.: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 527.

lesions present were not of the wire loop pattern, but the specificity of the latter is doubted. The valve lesions did not resemble those usually observed in atypical verrucous endocarditis, but certainly were not those encountered in rheumatic fever or in bacterial endocarditis. Absence of a characteristic eruption was the chief obstacle in establishing a diagnosis of lupus erythematosus disseminatus in our case, and yet the abundance of the other clinical and pathologic features points strongly to this disease. It may be justifiably concluded that in a case of a disease with such a variable picture, even at autopsy, the lack of one frequent sign should not preclude a diagnosis of that disorder.

SUMMARY

A consideration of the complex clinical manifestations of lupus erythematosus disseminatus is combined with the report of a case in which the patient exhibited pronounced pulmonary signs and lesions but showed no cutaneous eruptions at any time.

URIC ACID PARTITION IN GOUT AND IN HEPATIC DISEASE

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The problem of solubility of uric acid and urates in body fluids has been the subject of extensive studies. Uric acid is weak and dissolves in water in small amounts only. Sodium urate is more easily soluble,[1] but its solubility is depressed by the addition of sodium chloride. A physiologic solution of sodium chloride dissolves only one tenth of the amount soluble in distilled water.[2] The solubility of sodium urate in body fluids is much higher, however, than the determination of its solubility in physiologic solution of sodium chloride would suggest. Schade and Boden [3] observed that sodium urate solutions were characterized by properties specific for colloidal solutions, such as opalescence, gel formation and the Tyndall phenomenon (see also Bechhold and Ziegler [4]). This suggested the existence of a colloidal form of uric acid in body fluids (compare, however, Hoeber [5]). Freundlich and Farmer-Loeb [6] examined the electrical conductivity of sodium urate solutions and noted the presence of sodium ions, urate ions, undissociated noncolloidal sodium urate, colloidal neutral urate and colloidal urate ions. All these constituents of the sodium urate solution are in a state of equilibrium, which may vary according to concentration, acidity, temperature, etc.

From the Medical Services, the Nutrition Clinic, the Department of Chemistry Laboratories of Mount Sinai Hospital.

1. His, W., and Paul, T.: Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen, Ztschr. f. physiol. Chem. **31**:1 and 64, 1900.

2. Kohler, R.: Die Ausfallsbedingungen der Urate in tierischen Flüssigkeiten, Ztschr. f. klin. Med. **87**:190-200, 1919.

3. Schade, H., and Boden, E.: Ueber die Anomalie der Harnsäurelöslichkeit (kolloide Harnsäure), Ztschr. f. physiol. Chem. **83**:347, 1913.

4. Bechhold, H., and Ziegler, J.: Vorstudien über Gicht: III, Biochem. Ztschr. **64**:471-489, 1914.

5. Hoeber, R.: Physikalische Chemie der Zelle und der Gewebe, Leipzig, Wilhelm Engelmann, 1924, pp. 81-88.

6. Freundlich, H., and Farmer-Loeb, L.: Harnsäures Natrium als Kolloidelektrolyt, Biochem. Ztschr. **180**:141-155, 1927.

The recognition of the colloidal properties of uric acid solutions offered to the clinician plausible explanations for various clinical observations, particularly in regard to the excretion of uric acid, gout and the formation of uric acid calculi.

Regardless of certain controversies about the colloidal state of uric acid in body fluids, clinical observations led years ago to the assumption of "free" and "bound" uric acid. To the best of our knowledge, it was Minkowski [7] who first postulated the existence of combined uric acid in blood; on the basis of further experimental evidence, he reiterated his opinion more than thirty years later, in his last review of the subject.[8] Benedict and his co-workers [9] succeeded in isolating from the blood of various species of animals and from human blood a compound of one molecule of uric acid with one molecule of dextrorotatory ribose. It was assumed that this substance derives either from inosinic acid by oxidation of the hypoxanthine component or from guanylic acid by oxidation of the guanine moiety. According to Peters and Van Slyke,[10] this is the only organic combination of uric acid in the animal body the existence of which has been definitely proved (compare also Bornstein and Griesbach [11]). Fischer and Helferich, cited by Minkowski,[8] expressed a belief in the existence in the organism of an easily hydrolyzable nucleoside of uric acid, the presence of which is difficult to demonstrate.

A few French authors attempted to differentiate free uric acid from combined uric acid. Guillaumin [12] determined the amount of free uric acid in the blood after preliminary precipitation as a silver salt and the total uric acid directly by the Folin method in the metaphosphoric acid filtrate. Chabanier, Lebert and Lobo-Onell,[13] employing compensatory dialysis, concluded that all uric acid in the blood was free, as it was

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7. Minkowski, O.: Untersuchung zur Physiologie und Pathologie der Harnsäure bei Säugethieren, Arch. f. exper. Path. u. Pharmakol. **41**:375, 1898.

8. Minkowski, O.: Gicht, in Klemperer, G., and Klemperer, F.: Neue deutsche Klinik, Berlin, Urban & Schwarzenberg, 1930, vol. 4, p. 183.

9. Davis, A. R.; Newton, E. B., and Benedict, S. R.: The Combined Uric Acid in Beef Blood, J. Biol. Chem. **54**:595, 1922. Newton, E. B., and Davis, A. R.: Combined Uric Acid in Human, Horse, Sheep, Pig, Dog and Chicken Blood, ibid. **54**:603, 1922.

10. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 424.

11. Bornstein, A., and Griesbach, W.: Ueber das Vorkommen von gebundener Harnsäure in Menschenblut, Biochem. Ztschr. **106**:190-193, 1920.

12. Guillaumin, C. O.: Sur l'acide urique sanguin, Bull. Soc. chim. biol. **4**: 177-190, 1922.

13. Chabanier, H.; Lebert, M., and Lobo-Onell: De l'état de l'acide urique dans le sérum sanguin, Compt. rend. Soc. de biol. **87**:1269, 1922.

entirely dialyzable. Delaville and Jones [14] were the first to use ultrafiltration; they determined the amount of free and of total uric acid in the serum by ultrafiltration before and after hydrolysis with 3 per cent sulfuric acid. Without giving details of their method, they reported for the serum of normal persons 70 per cent free and 30 per cent combined uric acid; in a single patient with gout and in a single patient with cirrhosis of the liver a reversal of this ratio was observed. Achard, Levy and Marinowski [15] compared the results of ultrafiltration with those of precipitation by trichloroacetic acid; in their brief communication they presented conclusions similar to those of Delaville and Jones. Khouri,[16] attacking this problem from a slightly different viewpoint, subjected the serum to hydrolysis with tenth-normal sulfuric acid before and after precipitation of the proteins with trichloroacetic acid; this method did not yield constant values for the free and the combined uric acid.

Von Przylecki, Grynberg and Szrajber [17] studied the combination of uric acid with proteins, such as casein, gelatin, albumin and globulin, by varying the acidity, the concentration of uric acid, etc. The combination of uric acid with these proteins was reversible, with dissociation prevailing in the sol state and combination in the gel state. The reversibility also depended on the nature of the proteins. Addition of such electrolytes as sodium chloride and magnesium chloride led to dissociation. According to these authors, uric acid may occur in the body fluids in three states: molecularly disperse, colloidally disperse and bound to proteins. An equilibrium exists among these three states depending on the colloidal state of the protein, the degree of dispersion and the presence of electrolytes. In another study, Grynberg and Kisiel [18] performed similar experiments with various fats and lipoids; there was no binding of uric acid with these substances at p_H 7.5 to 8.5. Bennhold [19] employed the method of electrocataphoresis for the study

14. Delaville, M., and Jones, M. C.: Le dosage de l'acide urique dans le plasma sanguin, Compt. rend. Soc. de biol. **92**:522, 1925. Jones, M. C.: Le taux de l'acide urique dans le plasma sanguin du sujet normal. Rapport entre l'acide urique libre et total, ibid. **93**:295, 1925.

15. Achard, C.; Levy, J., and Marinowski, Z.: Sur l'acide urique ultrafiltrable, Compt. rend. Soc. de biol. **3**:366, 1932.

16. Khouri, J.: Recherches sur l'acide urique libre et les complexes uricogènes du sérum sanguin, Bull. Acad. de méd., Paris **118**:291-293, 1937.

17. von Przylecki, S. J.; Grynberg, M. Z., and Szrajber, D.: Untersuchungen über die Bindung der Biokolloide: III. Harnsäure-Eiweisskörper, Biochem. Ztschr. **244**:190, 1932.

18. Grynberg, M. Z., and Kisiel, S.: Untersuchungen über die Bindung der Biokolloide: VIII, Biochem. Ztschr. **253**:146-151, 1932.

19. Bennhold, H.: Vehikelfunktion der Bluteiweisskörper, in Bennhold, H.; Kylin, E., and Rusznyak, S.: Die Eiweisskörper des Blutplasmas, Dresden, Theodor Steinkopff, 1938, p. 255.

of free and of bound uric acid. From his experiments he concluded that uric acid in the blood is partly free and partly loosely bound to albumin and that an equilibrium exists between these two fractions. With diminishing concentration of free uric acid, the bound uric acid is set free.

The question as to the colloidal and the bound state of uric acid in serum has not been settled by studies of uric acid clearance. Brøchner-Mortensen [20] expressed the belief that uric acid in the blood does not exist in a colloidal or combined form but that it is a true threshhold substance, completely excreted by the glomeruli and probably partly reabsorbed by the tubules. Berglund and Frisk,[21] however, assumed that part of the uric acid is in a nonfiltrable form, that only the free uric acid passes the kidney and that no reabsorption from the filtrate occurs. An important point in all these considerations is the dialyzability and ultrafiltrability of the uric acid in blood. However, dialysis and ultrafiltration represent materially different procedures, and each of them is apt to solve different problems (see section on dialysis studies).

Only the following reports on the behavior of uric acid during ultrafiltration of blood could be found. The exact procedure is not described in any of them, and altogether only a few normal subjects and a few subjects with a pathologic condition have been investigated. The results of Delaville and Jones [14] and of Achard, Levy and Marinowski [15] have just been referred to. In a recent paper, Lambie [22] presented a study of a single case of juvenile gout of obscure origin; ultrafiltration of the patient's serum revealed that only 28 to 37 per cent of the uric acid of the plasma was filtrable; however, after splenectomy 63 to 100 per cent of the uric acid could be recovered in the ultrafiltrate. The ultrafiltration was performed with a collodion membrane of unknown pore size. In 3 normal subjects used for comparison bound uric acid was not found.

In view of the lack of reliable data, we decided to study the partition of uric acid under normal and under pathologic conditions. After a series of experiments with dialysis, ultrafiltration was used exclusively in the studies reported here. This report deals first with the observations on normal subjects and subsequently with those on subjects with pathologic conditions, particularly gout and hepatic disease.

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20. Brøchner-Mortensen, K.: On Variations in the Uric Acid Clearance After Administration of Purine, with Special Reference to the Threshold Protein, Acta med. Scandinav. **99**:525-539, 1939.

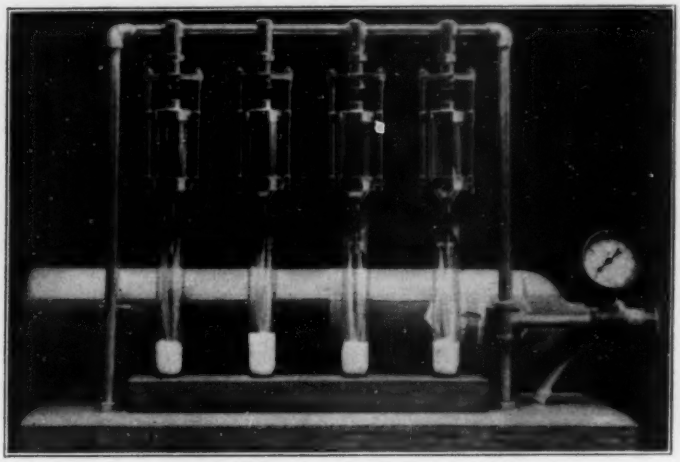
21. Berglund, H., and Frisk, A. R.: Uric Acid Elimination in Man, Acta med. Scandinav. **86**:233-267, 1935.

22. Lambie, C. G.: A Study of Juvenile Gout in a Patient Suffering from Chronic Erythronoclastic Anemia of Obscure Origin, Together with Observations upon Physical States of Uric Acid in Blood and Effects of Splenectomy, M. J. Australia **1**:535-558, 1940.

METHOD

The uric acid content of the blood serum was determined by the method of Benedict with the modification of Brown.[23] The blood proteins were removed by precipitation with tungstic acid. We agree with Jacobson[24] and others that the determination of uric acid in serum is preferable to that in whole blood.

The partition of uric acid was studied by ultrafiltration. In the tables the figures for free uric acid signify the acid in the ultrafiltrate, whereas those for bound uric acid represent the difference between the uric acid content of the tungstic acid filtrate (total uric acid) and the free uric acid. The following method of ultrafiltration was employed: Fresh serum was filtered through a "600" cellophane membrane at a pressure of 80 pounds (36 Kg.) of nitrogen per square inch (6 sq. cm.). The apparatus used was designed and built by Mr. J. Vondrak, of these laboratories (figure). We found it imperative to work under uniform condi-



Apparatus for the ultrafiltration of serum. Circular filters consisting of cellophane disks resting on metal sieve plates are situated at the bottom of four hermetically sealed heavy glass cylinders (inside diameter 29 mm.). The pressure is supplied from the tank of nitrogen conveniently placed in a horizontal position behind the cylinders. The arm leading from the tank to the manifold is supplied with a needle valve and a pressure gage. The filtrate drips into the graduated conical 15 cc. centrifuge tubes, which are held in position in the loosely stoppered 50 cc. centrifuge tubes. A case with heavy wired glass, fitting over the manifold and the four ultrafilters, is omitted in the photograph.

tions as far as the following factors were concerned: (*a*) duration of filtration, (*b*) amount of serum and of filtrate used and (*c*) handling of filtrate.

(*a*) To evaluate the time factor, specimens of the same sample of serum were filtered seven to sixty-five hours. The filtrates obtained in the course of seven to twenty-four hours showed practically identical composition, whereas filtrates

23. Brown, H.: Uric Acid in Blood, J. Biol. Chem. **68**:123-133, 1926.

24. Jacobson, B. M.: The Uric Acid in the Serum of Gouty and Non-Gouty Individuals, Ann. Int. Med. **11**:1277, 1938.

obtained after twenty-six to sixty-five hours varied considerably in uric acid content, for reasons not definitely determined. On the basis of these tests, all ultrafiltrations were carried out for eighteen to twenty-four hours. During this time an amount sufficient for uric acid analysis in duplicate is obtained.

(*b*) The smallest possible amount of serum had to be used because in some of these investigations a sample of blood had to be taken daily from the same subject, and in some instances, several times in the course of one day. Four cubic centimeters of serum proved sufficient to yield 1.5 cc. of ultrafiltrate within eighteen to twenty-four hours.

(*c*) The ultrafiltrate obtained under the aforementioned conditions is a slightly cloudy and turbid fluid. A series of tests was performed to determine the nature of the cloudiness and the influence of this factor on uric acid analysis. Biuret

TABLE 1.—*Effect of Centrifuging on the Uric Acid Content of Ultrafiltrates of Human Serum*

Subject No.	Total Uric Acid, Mg./100 Cc.	Uric Acid in the Ultrafiltrate, Mg./100 Cc.	
		Supernatant Fluid	Sediment
401	5.6	2.9	5.2
402	4.3	2.3	4.1
403	5.5	3.1	4.8

TABLE 2.—*Effect of the Addition of Chloroform on the Uric Acid Content of Ultrafiltrates of Human Serum*

Subject No.	Total Uric Acid, Mg./100 Cc.	Uric Acid in the Ultrafiltrate, Mg./100 Cc.	
		Without Chloroform	With Chloroform
404	4.7	4.2	4.0
405	5.5	4.8	4.4
406	5.7	4.4	4.1
Mixed serum	5.9	4.8	4.7

and sulfosalicylic acid reactions of the filtrate were negative. Microscopic examination revealed numerous saprophytic bacteria as cause of the turbidity. It was possible to centrifuge them off and thus to obtain a clear supernatant fluid. However, the uric acid content of this supernatant fluid was considerably lower than that of the residue. Table 1 illustrates the results of centrifugation. It is therefore imperative to avoid centrifuging and, on the contrary, to stir up the ultrafiltrate, thus providing equal distribution of the uric acid.

In a group of experiments we tried to prevent the growth of bacteria in the ultrafiltrates and compared the uric acid content of sterile ultrafiltrates and that of unsterile controls of the same sample of serum. The first series was performed with the addition of 1 to 2 drops of chloroform to the ultrafiltrate. The chloroform had no effect whatsoever on the growth of bacteria, but there was a small decrease of uric acid content in the chloroform-containing specimens (table 2). Instead of using other disinfectants to prevent bacterial growth, we examined a series of serums under sterile conditions. The sterility was tested at every step of the procedure. The sterile ultrafiltrates were water clear and showed no sediment after centrifuging. The nonsterile ones appeared mildly cloudy, as just

described. This proved that the cloudiness of the ultrafiltrates is due to bacterial growth and can be prevented by sterile handling. It is evident from the results summarized in table 3 that the nonsterile controls contained the same amounts of uric acid as the sterile ultrafiltrates, provided the former were not centrifuged prior to analysis.

The presence of bacteria in the ultrafiltrate does not interfere with the determination of uric acid. Precautions for maintaining strict sterility may thus be omitted as superfluous, besides being time-consuming and injurious to the permeability of the membranes.

DIALYSIS STUDIES

Three samples of serum, with a uric acid content varying from 3.7 to 8.4 mg. per hundred cubic centimeters, were dialyzed in cellophane bags [25] from two to four days against running tap water. Lithium urate was added in varying amounts to a specimen of each sample, raising the uric acid content before dialysis to 10.7, 14.0 and 24.5 mg. per hundred

TABLE 3.—*Effect of Sterilization on the Uric Acid Content of Ultrafiltrates of Human Serum*

Subject No.	Total Uric Acid, Mg./100 Cc.	Uric Acid in the Ultrafiltrate, Mg./100 Cc.	
		Nonsterile	Sterile
407	2.9	2.4	2.4
408	4.3	3.6	3.7
409	5.2	5.0	4.9
Mixed serum	5.8	5.3	5.3

cubic centimeters. After dialysis, no uric acid was found in the original samples or in the specimens in which the uric acid had been increased.

In a separate experiment a normal subject received 480 mg. of uric acid by intravenous injection; specimens of blood were drawn before the injection and one-half hour and three, six and twenty-four hours afterward. The uric acid content rose from 4.3 to 8.0 mg. per hundred cubic centimeters half an hour after the injection and gradually dropped to 6.7, 6.0 and 5.0 mg. per hundred cubic centimeters, respectively, in the subsequent specimens. In all five specimens the uric acid was completely removed on dialysis, or traces of less than 0.04 mg. per hundred cubic centimeters remained after twenty-four hours.

It was mentioned in a preceding paragraph that the equilibrium between free and combined uric acid is labile and can easily be disturbed by various factors, e. g., dialysis. Apparently, dialysis removes first the available free uric acid. This disturbs the equilibrium, and more uric acid is liberated, becomes dialyzable and is removed in turn from the

25. Visking sausage casing.

serum. Hence, dialysis is not suitable for the study of uric acid partition in protein-containing fluids (compare the statement of Freundlich and Farmer-Loeb [6]).

URIC ACID PARTITION IN NORMAL HUMAN SERUM

The range of the total uric acid and the ultrafiltrable and the non-ultrafiltrable fractions was established by a series of determinations on

TABLE 4.—*Uric Acid Partition in Normal Subjects*

Subject No.	Condition	Date	Total Uric Acid, Mg./100 Cc.	Uric Acid Partition		Bound Uric Acid, Percentage of Total Uric Acid
				Filtrable, Mg./100 Cc.	Non-filtrable, Mg./100 Cc.	
1	Duodenal ulcer	2/20/41	4.2	3.8	0.4	9
		2/25/41	4.0	3.3	0.7	18
		3/ 1/41	4.8	3.8	1.0	21
2	Old coronary artery occlusion	2/18/41	6.1	5.3	0.8	13
		2/21/41	6.8	5.5	1.3	19
		2/26/41	5.2	4.3	0.9	17
3	Congenital heart disease	2/17/41	3.4	2.8	0.6	18
		2/20/41	2.6	2.2	0.4	15
		2/25/41	3.0	2.5	0.5	17
4	Duodenal ulcer	2/18/41	4.1	3.3	0.8	19
		2/21/41	6.2	5.2	1.0	16
5	Normal	9/ 9/40	5.7	4.4	1.3	23
		1/13/41	5.2	4.1	1.1	21
6	Normal	9/13/40	5.1	3.9	1.2	24
		3/ 1/41	4.0	3.2	0.8	20
7	Obesity	3/ 5/41	5.2	4.2	1.0	19
		3/19/41	5.0	3.9	1.1	22
8	Duodenal ulcer	9/ 8/40	4.8	4.4	0.4	8
9	Thromboangiitis obliterans	9/ 8/40	6.1	5.1	1.0	16
10	Postural hypotension	9/ 8/40	6.6	5.8	0.8	12
11	Typhus (Brill's disease)	9/ 9/40	5.3	4.4	0.9	17
12	Normal	9/ 8/40	5.6	5.0	0.6	11
13	Angina pectoris	9/ 9/40	6.0	4.9	1.1	18
14	Arteriosclerotic heart disease	9/15/40	4.7	4.2	0.5	11
15	Sinusitis	9/15/40	5.5	4.8	0.7	13
16	Arteriosclerotic heart disease	9/18/40	5.7	4.4	1.3	23
17	Jejunal ulcer	9/24/40	4.5	3.6	0.9	20
18	Convalescence from pneumonia	10/29/40	4.3	3.6	0.7	16
19	Peptic ulcer	11/ 5/40	5.2	5.0	0.2	4
20	Abortion	11/ 8/40	3.4	3.1	0.3	9
21	Scleroderma	12/18/40	6.8	5.8	1.0	15
22	Obesity	3/ 5/41	4.6	3.7	0.9	20
Average			5.0	4.2	0.8	16

normal subjects. These consisted of 3 healthy volunteers and of patients convalescing from various diseases who were free of clinical symptoms. A few suffered from chronic conditions, such as peptic ulcer, obesity and compensated heart disease. Six of a total of 22 subjects were tested a second time after the experiments recorded in table 4, and in turn, 3 of these 6 were tested a third time.

The uric acid content of the serum varies from 2.6 to 6.8 mg. per hundred cubic centimeters. Compared with a series of one hundred

determinations by Jacobson [24] of uric acid in serum the lowest values in the present series are moderately higher than the lowest figures reported by this author (1.8 mg. per hundred cubic centimeters), but the upper limit is practically the same in both series. The average recorded by Jacobson was 4.2 per hundred cubic centimeters, compared to 5.0 mg. per hundred cubic centimeters obtained in the present investigation.

The ultrafiltrable fraction of the serum uric acid ranges from 2.2 to 5.8 mg. per hundred cubic centimeters, with an average of 4.2 mg. The nonfiltrable bound uric acid ranges from 0.2 to 1.3 mg. per hundred cubic centimeters, with an average of 0.8 mg. Expressed in percentage of the total uric acid, the bound uric acid averages 16 in normal subjects, with a range from 4 to 24.

Only in subject 1 the bound uric acid ranged from 9 to 21 per cent. The percentage of bound uric acid varied less even in much longer periods in the other subjects, for instance, from 13 to 19 in subject 2 and from 20 to 24 in subject 6. The uric acid partition is apparently stable in the serum of a given person.

URIC ACID PARTITION IN PATIENTS WITH MISCELLANEOUS PATHOLOGIC CONDITIONS

The uric acid partition in patients with various pathologic conditions was subsequently examined. We were guided by two viewpoints in the selection of subjects: First, we wished to survey all important disease groups, such as pulmonary, cardiovascular, renal and hepatic diseases and diseases of the blood, and second, we were interested in conditions known to be associated with disturbance of the purine metabolism, such as gout, uremia and forms of leukemia. It soon became evident that hepatic disease and gout may produce an anomalous picture. Hence, larger groups of patients with these diseases were examined and will be discussed in subsequent sections.

Table 5 presents the results of study of these patients with the exception of those with gout and hepatic disease. Normal values for total, as well as for bound, uric acid were encountered in the following patients: 101, with acute cellulitis of the leg; 102, with typical allergic bronchial asthma, and 108, with nephrotic hypoproteinemia, with total protein values varying from 3.4 to 5.2 Gm. per hundred cubic centimeters and inversion of the albumin-globulin ratio. Four persons with diabetes, (patients 114 to 117), 1 with ketosis, showed no abnormalities except a slightly elevated bound uric acid ratio of 26 per cent in patient 116.

In the following conditions elevated values for total uric acid were associated with a normal partition: uremia with marked azotemia

(patients 106 and 107), lymphatic leukemia (patients 118, 119 and 120), myeloid leukemia (patient 121), myasthenia gravis (patient 125) and amyotrophic lateral sclerosis (patients 122, 123 and 124).

The serum uric acid in patients with exophthalmic goiter behaved normally except in a patient suffering from a peculiar form of persistent

TABLE 5.—*Uric Acid Partition in Patients with Miscellaneous Pathologic Conditions Other Than Hepatic Disease or Gout*

Subject No.	Condition	Date	Total Uric Acid, Mg./100 Cc.	Uric Acid Partition		Bound Uric Acid, Percentage of Total Uric Acid
				Filtrable, Mg./100 Cc.	Non-filtrable, Mg./100 Cc.	
101	Cellulitis of leg	10/29/40	4.8	4.3	0.5	10
102	Bronchial asthma	10/29/40	2.9	2.4	0.5	17
103	Bronchiectasis	11/12/40	7.2	5.5	1.7	24
104	Acute coronary artery occlusion	10/29/40	7.4	7.0	0.4	5
105	Pyloric obstruction	1/ 3/41	4.6	3.7	0.9	20
106	Uremia	11/17/40	8.0	7.1	0.9	11
107	Uremia	11/17/40	15.6	14.9	0.7	5
108	Nephrosis; hypoproteinemia	11/12/40	4.4	4.0	0.4	9
109	Persistent hyperthyroidism	11/24/40	5.1	2.6	2.5	49
		11/26/40	5.1	4.5	0.6	12
110	Exophthalmic goiter	11/27/40	6.6	5.6	1.0	15
111	Exophthalmic goiter	12/ 8/40	5.5	4.4	1.1	20
112	Exophthalmic goiter	12/ 8/40	3.3	2.8	0.5	15
113	Exophthalmic goiter	12/25/40	6.2	5.4	0.8	13
114	Diabetes	11/ 8/40	2.8	2.2	0.6	21
115	Diabetes	11/ 8/40	3.3	2.9	0.4	12
116	Diabetes	12/ 1/40	5.3	3.9	1.4	26
117	Diabetes; ketosis	12/18/40	4.4	3.9	0.5	11
118	Lymphatic leukemia	12/ 2/40	5.7	4.9	0.8	14
119	Lymphatic leukemia	12/ 8/40	5.6	4.6	1.0	18
120	Lymphatic leukemia	12/25/40	3.1	2.4	0.7	23
121	Myeloid leukemia	12/ 2/40	7.2	5.7	1.5	20
122	Amyotrophic lateral sclerosis	11/10/40	8.0	7.2	0.8	10
123	Amyotrophic lateral sclerosis	11/10/40	10.5	8.4	2.1	20
124	Amyotrophic lateral sclerosis	11/10/40	10.5	8.5	2.0	19
125	Myasthenia gravis	11/10/40	6.9	6.2	0.7	10
126	Multiple myeloma	11/14/40	9.8	6.3	3.5	36
		11/24/40	8.6	5.4	3.2	37
127	Multiple myeloma	4/ 9/41	6.1	5.5	0.6	10

hyperthyroidism or possibly a hypothalamic lesion, who exhibited active symptoms of the disease in association with unusual muscular disturbances. Because of its peculiarities, a short abstract of the history will follow.

B. M., a 29 year old man, had an episode of polydipsia, diarrhea, a gain of 100 pounds (45 Kg.) within six months and dropping of the left eyelid eight years prior to admission. A year and a half before he followed a strict diet, with a loss of 100 pounds in six months. Toward the end of this period he displayed symptoms of hypermetabolism, and his basal metabolic rate was + 60 per cent.

After the administration of compound solution of iodine U. S. P. his basal metabolic rate decreased to + 30 per cent. A subtotal thyroidectomy was performed. One month after operation symptoms recurred, with weakness, tachycardia and sweating. For the past year and a half he had had attacks of intermittent paralysis of the upper and lower extremities lasting eight to ten hours. On occasion these were accompanied by nausea, vomiting, diarrhea and incontinence.

On physical examination he appeared well nourished and overactive. Ptosis of the left eyelid, slight exophthalmos, lidlag and stare were present. The blood pressure was 140 systolic and 80 diastolic. There was slight nystagmus on looking to the left.

Laboratory examination yielded the following data: The blood urea nitrogen was 10 mg. per hundred cubic centimeters; the total cholesterol in the blood, 155 mg. per hundred cubic centimeters; the esterified cholesterol, 55 mg. per hundred cubic centimeters; the result of the galactose tolerance test, 1.1 Gm.; the Wassermann reaction, negative, and the basal metabolic rate, + 43 and + 52 per cent.

Inasmuch as thyroidectomy had been almost complete and there was no evidence of any substernal extension of the thyroid, it was believed that the hypermetabolism was not due to hyperthyroidism but possibly to hypothalamic lesion following encephalitis.

In contrast, 4 other patients with exophthalmic goiter, with and without medication with iodine, showed a normal uric acid picture.

The next to the last patient in table 5 (patient 126) had values which showed marked deviation from the normal figures both for total and for bound uric acid. A summary of his history follows:

A 46 year old man had multiple myeloma with loss of weight, pallor and bleeding from the gums for four weeks prior to admission. The liver and the spleen were enlarged. There was marked secondary anemia, with 2,100,000 red cells per cubic millimeter and a hemoglobin concentration of 23 per cent; Bence Jones protein was found in the urine. Typical bone changes were observed on roentgen examination.

The serum of this patient was of syrup-like appearance and of abnormally high viscosity. The total protein content rose gradually from 7.4 to 11.6 Gm. per hundred cubic centimeters, with 3.2 Gm. of albumin and 8.4 Gm. of globulin. The total uric acid content was 8.6 to 9.8 mg. per hundred cubic centimeters, the bound uric acid ratio on two occasions being 36 and 37 per cent, respectively. A second person (patient 127) with this disease but without hyperproteinemia displayed a normal uric acid picture.

The uric acid partition does not deviate from that of normal persons, with the exception of values for the aforementioned patients with atypical exophthalmic goiter and with multiple myeloma, the significance of which will be discussed later. The total uric acid in the serum is elevated in patients with uremia and amyotrophic lateral sclerosis, resulting in a comparatively high average value for the entire group given in table 5,

namely, 6.2 mg. per hundred cubic centimeters. The bound uric acid ratio averages 15 per cent of the total uric acid, which coincides with the value given for normal uric acid partition.

URIC ACID PARTITION IN PATIENTS WITH HEPATIC DISEASE

Changes of uric acid metabolism have frequently been reported in patients with hepatic disease. Robecchi and Muttini [26] reported low values for uric acid in the blood of patients with hepatic disease and a return to normal figures on clinical improvement. They also observed retarded elimination and a delayed "uric acid curve" in serum after intravenous injection of this substance. Similar observations were made on patients with gout. On the other hand, Chrometzka [27] reported high figures for uric acid in patients with hepatitis. Brøchner-Mortensen [28] found increased values for uric acid in the blood of patients with disease of the liver and the biliary system. In those with the severest hepatic damage, hyperuricemia did not occur. In spite of a few contradictory findings, one gains the impression that obstructive jaundice leads to an elevation of uric acid content but that hepatic damage, at least in severe degrees, leads to low values. In the present series, a low titer of uric acid in the blood was met with only in patients with icterus of long duration and possible secondary hepatic damage (carcinoma of the pancreas, cholangitis with pylephlebitis). Patients with hepatitis and cirrhosis of the liver presented no consistent change in the total uric acid content of the blood.

The present group, summarized in table 6, consists of 28 patients with hepatic disease, namely, 8 with toxic hepatitis, 10 with cirrhosis of the liver, 3 with carcinoma of the head of the pancreas with obstructive jaundice and 1 each with cholangitis, biliary cirrhosis, carcinoma of the gallbladder, cholelithiasis with superimposed toxic hepatitis, cholelithiasis complicated by suppurative cholangitis and pylephlebitis, lymphatic leukemia and metastatic carcinoma superimposed on cirrhosis of the liver.

In the largest subgroup, represented by cirrhosis of the liver, the total content of uric acid varies from 2.9 to 7.5 mg. per hundred cubic centimeters (patients 208 to 217). The average of 4.6 mg. per hundred cubic centimeters is comparable with the normal average of 5.0 mg. The uric acid partition in the first 5 patients (208 to 212), having values for bound uric acid ranging from 8 to 24 per cent of the total uric acid,

26. Robecchi, A., and Muttini, C.: Studi sul metabolismo purinico; il ricambio purinico negli epato-pazienti, Arch per le sc. med. **65**:475-510, 1938.

27. Chrometzka, F.: Die zentrale Stellung der Leber im Purinstoffwechsel und ihre Bedeutung fuer die Pathogenese der Gicht, Klin. Wchnschr. **51**:1877, 1936.

28. Brøchner-Mortensen, K.: The Uric Acid in Blood and Urine in Health and Disease, Medicine **19**:161-229, 1940.

may be considered normal. The values for the other 5 patients, 213 to 217, differ from the normal picture by at least one bound uric acid ratio above 24 per cent during repeated examinations. All these patients show in the course of their illness normal figures changing into abnormal ones or vice versa. Thus, the value of 27 per cent bound uric acid in patient 213 decreased to 7 per cent within one week; the change was accompanied by clinical improvement, probably due to extensive therapy. In contrast, patient 215, starting with a normal uric acid partition, showed an elevation of the bound uric acid ratio during progressive deterioration of the general condition, which led to a fatal outcome. It is impossible to decide on the basis of the present observations why patients with cirrhosis may in some instances present these transient changes of uric acid partition. One has to consider that the patients with normal uric acid partition have been examined only once, with 1 exception, so that a temporary deviation of the uric acid partition could easily have been missed. It is plausible that these fluctuations are connected with episodes of acute exacerbation in the course of the disease.

In the subgroup of 8 patients with toxic hepatitis the total uric acid content ranges between 2.6 and 6.2 mg. per hundred cubic centimeters, averaging 4.7 mg., a normal value. In 5 persons (patients 222, 223, 224, 227 and 228) the uric acid partition is entirely normal, with bound uric acid ratios between 11 and 21 per cent. Four of these patients have been examined during improvement of the general condition and subsiding icterus. The fifth one (patient 227) had long-lasting but mild hepatitis. In the other 3 persons (patients 221, 225 and 226) normal values for total uric acid are associated with abnormal uric acid partition, up to 41 per cent bound uric acid. One of these patients was examined three times during the course of her illness. At the height of the disease and impairment of hepatic function, a disturbance of uric acid partition prevailed, while uric acid partition was normal at the onset and during recovery. The present material is too scant to permit definite conclusions as to the relation between hepatic function and uric acid partition.

The next subgroup is represented by 4 persons with malignant growths (patients 202, 203, 204 and 205) characterized by icterus of long duration, enlargement of the liver and considerable loss of weight. In 3 patients the diagnosis was confirmed by operation. In 2 patients of this group, the total uric acid is low. The uric acid partition is normal only in patient 202 and abnormal in the others, in whom the bound uric acid ranges between 31 and 40 per cent of the total uric acid. The highest figure, 40 per cent, is found in patient 205, in whom the total uric acid is only 2 mg. per hundred cubic centimeters. That low values for total uric acid are not necessarily accompanied by relatively high

TABLE 6.—*Uric Acid Partition in Patients with Hepatic Disease*

Patient No.	Sex; Age, Yr.	Condition	Date	Uric Acid Partition: Total Uric Acid, Mg./100 Cc.	Uric Acid Partition: Filtrable, Mg./100 Cc.	Uric Acid Partition: Nonfiltrable, Mg./100 Cc.	Bound Uric Acid, Percentage of Total Uric Acid	Laboratory Data: Icteric Index	Laboratory Data: Cholesterol, Mg./100 Cc. Total	Laboratory Data: Cholesterol, Mg./100 Cc. Ester	Laboratory Data: Galactose Tolerance, Gm.	Clinical Data
201	♀ 42	Cholelithiasis; toxic hepatitis; diabetes mellitus	11/17/40	4.2	3.7	0.5	12	94	195	45	7.1	Diabetes 4 mo. and icterus and chills 3 days before admission; liver palpable 3 fingerbreadths below costal margin; 2 biliary calculi in cholecystogram; positive reaction for tyrosine in urine; gradual improvement
202	♂ 59	Carcinoma of head of pancreas; diabetes mellitus	11/14/40	5.6	4.8	0.8	14	24	250	130	...	Diabetes 2 yr. and progressive painless jaundice a few days before admission; exploration: hard mass in head of pancreas, no gallstones
203	♀ 63	Carcinoma of gallbladder; diabetes; hypertension	1/ 8/41	3.7	2.5	1.2	32	17	...	..	...	Jaundice 4 wk. before admission; liver palpable 3-4 fingerbreadths below costal margin; laparotomy; carcinoma of gallbladder; blood sugar, 310 mg./100 cc.; blood total protein, 7.1 Gm./100 cc.
204	♂ 70	Carcinoma of head of pancreas; diabetes	1/27/41	2.9	2.0	0.9	31	21	170	90	...	Loss of weight; icterus; liver palpable 4 fingerbreadths below costal margin; phosphatase, 58 King-Armstrong units
205	♂ 58	Carcinoma of head of pancreas; tertiary syphilis	1/24/41	2.0	1.2	0.8	40	45	400	..	3.5	Syphilis for many years; pain, loss of weight and anorexia 3 mo. before admission; operation: large firm mass in head of pancreas and greatly extended gallbladder, containing 500 cc. of white bile
206	♀ 55	Pylephlebitis; suppurative cholangitis; cholelithiasis	9/19/40	2.6	1.4	1.2	46	45	170	50	...	Recurrent pain in right upper quadrant of abdomen for 20 yr.; episode of pain, with chills, fever, vomiting and icterus 2-3 wk. before admission; autopsy: pylephlebitis, thrombotic occlusion of portal vein, perforation of gallbladder and pericholecystic abscess; temperature 103-106 F.
207	♀ 52	Cholangitis; cholangiolitis	12/29/40 1/10/41	3.8 4.6	3.0 4.0	0.8 0.6	21 13	..	...	..	...	Cholecystectomy 5 yr. ago; painless increasing jaundice and dark urine 3 wk. before admission; loss of weight; temperature, 101 F.; small shrunken gallbladder; common duct dilated to about ¾ in. in diameter; no evidence of stones; biopsy of liver: acute and chronic cholangiolitis and pericholangiolitis, no evidence of cirrhosis; biopsy of common duct: chronic and acute inflammation of wall
208	♂ 48	Cirrhosis of liver; syphilis; psoriasis; pyelonephritis	9/12/40	7.3	6.7	0.6	8	8	125	65	4.7	Syphilis for 20 yr.; ascites, edema, hematemesis and melena 3 days prior to admission; liver and spleen enlarged; Takata-Ara reaction positive (++++); test for bilirubin in urine negative
209	♂ 65	Cirrhosis of liver; macrocytic anemia	9/12/40	6.7	5.8	0.9	13	9	230	145	2.9	History of gallbladder disease for 20 yr.; painful jaundice 10 yr. ago; liver palpable 4 fingerbreadths below costal margin; spleen enlarged
210	♂ 33	Cirrhosis of liver	9/22/40	2.9	2.2	0.7	24	15	170	60	...	Second admission because of reaccumulated ascites and severe edema of lower extremities; cachexia; liver and spleen palpable; total protein in blood, 5.6 Gm./100 cc.; positive reaction for bilirubin in urine
211	♂ 38	Cirrhosis of liver; toxic hepatitis	11/12/40 12/11/40	4.1 4.6	3.4 3.6	0.7 1.0	17 22	20	190	70	...	Addicted to alcohol since age of 7; edema for 4 wk. and jaundice and acholic stools 3 wk. before admission; loss of 35 lb. in 8 mo.; liver enlarged to umbilicus; spleen palpable 2 fingerbreadths below costal margin; necropsy: Laennec's cirrhosis; Wassermann reaction positive (++++)
212	♂ 43	Cirrhosis of liver; syphilis	11/21/40	5.6	4.4	1.2	21	..	...	..	9.7	Gonorrhea and syphilis 18 yr. before admission, with many specific treatments since; jaundice of 5 mo. duration during antisyphilitic therapy 1 yr. before admission; tarry stools 1 day before admission; liver palpable 1½ fingerbreadths below costal margin; no ascites; Wassermann reaction positive (++++)
213	♀ 26	Cirrhosis of liver	12/17/40 12/23/40	3.3 2.8	3.4 2.6	0.0 0.2	97 7	28 ..	625 500	80 65	1.9	Addicted to alcohol for 3 yr.; ascites and edema; alcoholic polyneuritis; liver enlarged; gradual improvement
214	♀ 43	Cirrhosis of liver	1/15/41 1/24/41	3.8 3.8	3.1 2.8	0.7 1.0	18 26	9	335	155	...	Attacks of hunger, weakness, sweating, palpitation and anxiety; nodular liver, palpable down to umbilicus; hard sharp

liver; syphilis

213	♀ 26	Cirrhosis of liver	12/17/40 12/23/40	3.3 2.8	2.4 2.6	0.9 0.2	27 7	28 ..	675 500	80 65	1.2	Addicted to alcohol for 3 yr.; ascites and edema; alcoholic polyneuritis; liver enlarged; gradual improvement
214	♀ 43	Cirrhosis of liver	1/15/41 1/24/41	3.8 3.8	3.1 2.8	0.7 1.0	18 26	9	335	155	...	Attacks of hunger, weakness, sweating, palpitation and anxiety; nodular liver, palpable down to umbilicus; hard sharp spleen
215	♀ 45	Cirrhosis of liver; subacute bacterial endocarditis	1/16/41 1/28/41 2/ 7/41	4.3 3.6 3.9	3.6 2.7 2.7	0.7 0.9 1.2	16 25 31	25	225	75	...	Ascites, edema; progressive impairment of general condition; positive reaction for tyrosine in urine; blood content (mg./100 cc.) of total protein 5.6, albumin 2.5, globulin 3.1; death from cholemia; autopsy: Laennec's cirrhosis of liver, splenomegaly, dilatation of esophageal veins and subacute bacterial endocarditis of aortic valve superimposed on chronic rheumatic valvulitis
216	♀ 33	Cirrhosis of liver	1/19/41 1/31/41	7.5 6.7	6.2 5.0	1.3 1.7	17 25	14	405	190	5.3	Liver palpable 2-3 fingerbreadths above umbilicus; spleen palpable; no definite ascites; icterus slowly subsiding; general condition improved
217	♀ 44	Cirrhosis of liver; diaphragmatic hernia	1/ 2/41 2/ 5/41	3.6 3.4	2.0 2.8	1.6 0.6	44 18	8	300	175	5.6	Liver enlarged, spleen palpable; exploratory laparotomy: cirrhotic liver, hob-nailed in appearance; biopsy of liver: obliteration of lobular architecture with infiltration of periportal fields with plasma cells, lymphocytes and leukocytes, suggestive of early cirrhosis
218	♀ 60	Biliary cirrhosis of liver; obstructive jaundice of long duration	1/ 1/41 1/ 8/41 1/20/41	3.5 3.7 3.9	2.4 2.3 2.9	1.1 1.4 1.0	31 38 26	28 9	260	..	1.7	Cholecystectomy 2 yr. before admission; postoperative spontaneous biliary fistula; fever, chills, light stools and dark urine for several weeks; liver enlarged; biopsy: acute and chronic pericholangitis with fibrosis of the periportal fields; slow improvement
219	♂ 57	Metastatic carcinoma of liver; cirrhosis of liver	1/27/41	3.1	2.1	1.0	32	48	345	145	1.0	Heavy drinker until 9 yr. before admission; loss of weight, anorexia, icterus; mass in epigastrium; diagnosis proved by biopsy
220	♀ 54	Lymphatic leukemia; obstructive jaundice	12/12/40 12/27/40	8.8 4.8	6.3 3.8	2.5 1.0	28 21	40 13	... 285	..	... 2.45	Lymphatic leukemia of 1 yr. duration; nausea, dark urine and icterus 2 wk. prior to admission; liver 2½ fingerbreadths below costal margin, spleen enlarged to umbilicus; after roentgen therapy liver decreased in size, icterus subsided
221	♂ 19	Toxic hepatitis due to gold	12/ 5/40	5.2	3.7	1.5	29	34	190	70	4.6	Arthritis for 6 yr.; series of gold injections 8 wk. before admission; chills, temperature of 102 F. and progressive icterus 4 days before admission; liver palpable; icterus slowly subsiding
222	♂ 23	Hepatitis, subsiding	9/12/40	5.8	4.8	1.0	17	30	210	60	6.4	Yellow skin, light stool and dark urine 2 wk. before admission; liver hard, enlarged to point 1 fingerbreadth below costal margin; gradual improvement
223	♂ 37	Toxic hepatitis, subsiding	9/12/40	6.2	5.3	0.9	15	16	230	55	5.8	Anorexia, nausea and dark urine 11 days before admission; jaundice 3 days later; liver hard, enlarged; gradual improvement; positive reaction for bilirubin in urine
224	♀ 34	Toxic hepatitis due to cinchophen	11/ 8/40	3.6	3.2	0.4	11	9	135	25	4.3	Took acetylsalicylic acid and cinchophen for relief of sciatica; anorexia, icterus, pruritus; total dose of cinchophen, 64 grains in 5 days; examined in subsiding state; positive reaction for tyrosine in urine
225	♂ 31	Toxic hepatitis	1/12/40 1/17/40	5.8 5.8	4.9 4.0	0.9 1.8	16 31	26 12	280	155	Normal	Dysentery 6 mo. prior to admission; jaundice 3 mo. later; icterus subsiding
226	♀ 69	Hepatitis	1/20/41 1/28/41 2/ 5/41	6.1 4.1 4.3	5.1 2.4 4.0	1.0 1.7 0.3	16 41 7	85 70 35	190 170 200	..	1.5 8.3	Recurrent painless jaundice; icterus slowly subsiding; course complicated by infection caused by Bacillus coli; urinalysis: (1/20) positive reaction for bilirubin (+++) and urobilin (1:4), (1/28) positive reaction for bilirubin (++), (2/5) positive reaction for bilirubin
227	♀ 33	Hepatitis	1/22/41 1/30/41 2/ 7/41	2.6 3.4 3.2	2.2 2.7 2.7	0.4 0.7 0.5	15 21 16	70 45 21	170	30	2.4	Long-lasting, mild hepatitis, with complete remission of symptoms; urinalysis: (1/22) positive reaction for bilirubin (++++) and urobilin (1:4), (2/7) positive reaction for bilirubin and urobilin (1:10)
228	♂ 55	Hepatitis	12/27/40	5.1	4.1	1.0	20	44	...	..	...	Jaundice subsiding; no pain, no masses, liver not palpable; urinalysis: positive reaction for bilirubin and urobilin (1:80)

percentages of bound uric acid is evidenced by the values for persons without hepatic disease (subjects 3 and 19 in table 4 and patients 102, 112 and 114 in table 5). The long-lasting icterus and the associated hepatic damage must be responsible for the abnormalities of uric acid partition in the patients with carcinoma with biliary obstruction.

Among the other patients with hepatic disease, abnormal uric acid partition was observed but twice, once in a patient with suppurative cholangitis and pylephlebitis with severe icterus and a low titer of cholesterol ester. This patient, who died, had a total uric acid content of 2.6 mg. per hundred cubic centimeters and a bound uric acid value of 46 per cent (patient 206). The other patient had lymphatic leukemia (patient 220) with icterus, which subsided slowly on roentgen treatment of the liver. At the height of the disease, the total uric acid was elevated to 8.8 mg. per hundred cubic centimeters, and the bound uric acid was 28 per cent of the total. During recovery, when the icteric index decreased rapidly from 40 to 13 units, the total uric acid dropped to 4.8 mg. per hundred cubic centimeters and the bound uric acid to 21 per cent of the total.

URIC ACID PARTITION IN PATIENTS WITH GOUT

The significance of uric acid metabolism in the etiology of gout is a subject of controversy, but it is generally acknowledged that gout is associated with abnormalities of uric acid metabolism. In the course of almost two years we were able to observe 10 patients with typical gout. A few persons with atypical gout were purposely disregarded. The 10 patients selected had a history of periodic attacks of pain, particularly in the big toes, with reddening and swelling. They responded promptly to a purine free, low fat diet [29] plus administration of colchicine. The total uric acid in these patients (table 7) is markedly elevated and varies from 5.1 to 16.4 mg. per hundred cubic centimeters, the average for all patients being 9.2 mg. per hundred cubic centimeters, almost double the average value for total uric acid in the serum of normal persons. The high level of the total uric acid is associated with an elevation of the free uric acid to 14.4 mg. per hundred cubic centimeters, with an average of 7.4 mg. The bound uric acid ranges between 0.1 and 3.6 mg. per hundred cubic centimeters, with an average of 1.8 mg., which is double the average bound uric acid in normal persons. Yet in relation to the total uric acid, the bound uric acid averages 20 per cent, compared to a ratio of 16 per cent in normal serum. The patients in table 7 present a greater variety of values both for the total uric acid and for the uric acid partition than does any other group of our subjects.

29. Adlersberg, D., and Ellenberg, M.: Effect of Carbohydrate and Fat in the Diet on Uric Acid Excretion, J. Biol. Chem. **128**:379-385, 1939.

The observation of patients with gout over a prolonged period and the correlation of the findings with the clinical course are of interest. Patient 301 has been observed for half a year. His total uric acid is

TABLE 7.—*Uric Acid Partition in Patients with Gout*

Patient No.	Sex; Age, Yr.	Date	Total Uric Acid, Mg./100 Cc.	Uric Acid Partition: Filtrable, Mg./100 Cc.	Uric Acid Partition: Nonfiltrable, Mg./100 Cc.	Bound Uric Acid, Percentage of Total Uric Acid	Clinical Data
301	♂ 60	9/23/40	10.0	8.7	1.3	13	Lithopexy for vesical calculi February 1940; attacks of pain and swelling of right big toe, ankle and elbow for past few years; tophi on ears; prompt response to cholchicine
		11/28/40	10.7	9.4	1.3	12	
		1/ 2/41	10.8	8.2	2.6	24	
		1/ 4/41	10.4	9.0	1.4	14	
		1/18/41	11.6	10.2	1.4	12	
		2/ 6/41	10.0	8.3	1.7	17	
		3/29/41	11.6	10.0	1.6	14	
302	♂ 65	9/26/40	13.0	10.7	2.3	18	Polycythemia for 7 yr.; hemoglobin concentration, 110 per cent; red cell count, 7,750,000; numerous tophi over most of joints; multiple cysts of kidneys with deposition of uric acid revealed at necropsy
303	♂ 67	12/18/40	7.8	6.5	1.3	16	History of arthritis of big toe; good response to colchicine
304	♂ 51	12/23/40	5.8	4.0	1.8	31	Pain in feet for 4 yr., with redness and swelling; later swelling and redness of a few finger joints; prompt improvement on antigout regimen and colchicine therapy
		2/ 7/41	5.5	1.9	3.6	65	
		3/ 1/41	5.7	4.2	1.5	26	
305	♂ 50	12/29/40	16.4	14.4	2.0	12	Redness of skin of several days' duration, with cellulitis; knee swollen, red and painful and fever present during observation
306	♀ 50	1/ 6/41	5.6	4.2	1.4	25	Attacks of pain in right knee and both shoulders and fingers of both hands, particularly the right ones; improvement on low purine, low fat diet and colchicine therapy
		2/ 5/41	6.3	5.3	1.0	16	
307	♀ 64	1/12/41	6.0	4.4	1.6	27	Pain in right knee and foot; obesity; sudden pain in right toe, hypertension and arteriosclerosis; improvement on gout diet
		1/24/41	5.1	3.4	1.7	33	
308	♂ 48	1/13/41	9.0	6.4	2.6	29	Pains starting in left big toe, ankle and knee and swelling and redness for 10 yr.; tophi in ears; definite improvement on gout diet and colchicine therapy
309	♂ 54	1/ 6/41	9.5	7.1	2.4	25	Obesity; pain in left big toe and foot; improvement on therapy with mild mercurous chloride and sodium bicarbonate; erosion of head of fifth left metatarsal for about 5 mm. (tophus)
		1/24/41	9.6	7.5	2.1	22	
310	♂ 34	4/ 1/41	10.3	10.2	0.1	1	Attacks of swelling, tenderness and reddening of left ankle; obesity; improvement on gout regimen
		4/ 3/41	10.4	9.1	1.3	13	
		4/17/41	9.4	6.9	2.5	27	
		4/25/41	9.7	8.1	1.6	17	

considerably elevated, to 10.0 to 11.6 mg. per hundred cubic centimeters. The uric acid partition is fairly constant, the bound uric acid being 1.3 to 1.7 mg. per hundred cubic centimeters, or 12 to 17 per cent of the total uric acid. Only on one occasion, during an attack of gout, was there an elevation of the bound uric acid to 2.6 mg. per hundred cubic

centimeters, or 24 per cent of the total uric acid. On initiation of colchicine therapy the symptoms promptly subsided, and two days later and thereafter the uric acid partition was normal. The elevation of the level simultaneously with the attack is of interest, although the value of 24 per cent bound uric acid falls just within the upper limit of normal.

Patient 304 was examined three times. During the whole period he was never completely free of symptoms. Although the total uric acid content was normal, the uric acid partition was abnormal, particularly on the second examination. On this occasion the patient had only 1.9 mg. of free uric acid, as against 3.6 mg. of bound uric acid, per hundred cubic centimeters. The bound uric acid represented 65 per cent of the total uric acid, the only instance of a reversal of the ratio. The lowest figure for bound uric acid in this patient was 26 per cent. It is noteworthy that in this patient with typical gout a normal total uric acid content was associated throughout the period of observation with an abnormal uric acid partition. Patient 307 presents a similar picture, normal values for the total uric acid content but an abnormal bound uric acid ratio of 27 to 33 per cent. On the other hand, one should remember that hyperuricemia, even of an extremely high degree (13.0 and 16.4 mg. per hundred cubic centimeters) may be associated with a normal uric acid partition (18 and 12 per cent, respectively), as in patients 302 and 305.

In the normal group individual constancy of uric acid partition was noticed. On the contrary, in a patient with gout, the total uric acid content may remain quite constant, while the uric acid partition shows considerable fluctuation. This is exemplified by patients 301 and 304 and, in particular, patient 310. The last-named patient was admitted with severe pain in one foot and was given colchicine immediately. The first specimen of blood was drawn after four days of treatment and yielded a total uric acid content of 10.3 mg. per hundred cubic centimeters, with almost complete absence of bound uric acid; in other words, the entire uric acid content was ultrafiltrable, a unique finding. Three days later the bound uric acid had returned to the normal value of 13 per cent. Because of recurrence of pain a few days later, the patient was given cinchophen. The total uric acid content diminished moderately, and the bound uric acid increased to 27 per cent. After a second course of colchicine, the bound uric acid dropped to 17 per cent, with no change in the total uric acid content. We surmise that the beneficial effect of colchicine on uric acid diathesis is due to lowering of the bound, rather than of the total, uric acid titer.

A review of data on the patients with gout reveals (*a*) occurrence of the highest absolute figures for total, as well as for free and for bound, uric acid, (*b*) absence of parallelism between the degree of hyper-

uricemia and the disturbance of uric acid partition and (*c*) great variability in the amount of bound uric acid, probably connected with the clinical course of the disease and with therapeutic measures. We wish to emphasize that patients with typical gout, such as patients 304, 306 and 307, have normal figures for total uric acid but abnormally high values for bound uric acid. Under these circumstances the ratio may form a valuable criterion for the diagnosis of gout. This problem is the subject of further studies.

COMMENT

Consideration of the entire material presented in this paper permits the following statements: Comparatively constant uric acid partition is a characteristic of the normal blood serum. Among the pathologic conditions considered, particularly gout and hepatic damage bring about disturbance of the uric acid partition, characterized by a diminution of the free, and elevation of the bound, uric acid fraction. The liver is known to play an important role in purine metabolism; hence, hepatic disease may result in disturbances of this metabolic domain. Gout, in turn, may be accompanied by signs of hepatic damage. Whatever the primary disturbance of uric acid metabolism may consist of in hepatic disease, it manifests itself in a change of uric acid partition. Whether the analogous variations in persons with gout are caused by a dysfunction of the liver cannot yet be decided.

The real nature of the bound uric acid in the blood is as yet unknown. For the same reason, no further explanation can be offered for the elevation of this fraction in the patients with the pathologic conditions mentioned. Nevertheless, it is interesting to speculate on possible common etiologic factors in hepatic disease and gout. Further investigations will be required to establish the place and the importance of uric acid partition in clinical diagnosis along the suggested lines.

SUMMARY

In 22 normal subjects the nonultrafiltrable (bound) uric acid varied between 4 and 24 per cent of the total uric acid content of the serum, the average being 16 per cent. There is a certain individual constancy of uric acid partition.

In 25 patients with miscellaneous pathologic conditions the uric acid partition was normal. Abnormally high values for the nonultrafiltrable fraction occurred only in 1 patient with atypical exophthalmic goiter and in 1 with multiple myeloma.

Abnormal uric acid partition was observed in about half of the patients with hepatitis, cirrhosis of the liver and prolonged obstructive jaundice, also in a patient with suppurative cholangitis and in 1 with

leukemia with icterus. A high titer of bound uric acid is not a persistent finding in the individual patient with hepatic damage. Clinical improvement may be associated with a decrease of bound uric acid and vice versa.

In 10 patients with gout, elevation of total, and correspondingly of bound, uric acid prevailed. The bound uric acid varied from 1 to 65 per cent of the total uric acid content. Gout with extreme hyperuricemia may be associated with a normal uric acid partition; on the other hand, patients with gout in whom the total uric acid content is not elevated may be distinguished by a high bound uric acid ratio. The diagnostic significance of such findings is suggested. A possible relation between the clinical course, the therapeutic measures and the bound uric acid fraction is discussed.

Dr. Max Ellenberg and Miss Lena Sharney assisted in obtaining and analyzing some of the specimens.

MULTIPLE POLYPS OF THE ESOPHAGUS

REPORT OF A CASE WITH COMPLICATING RECURRENT GASTROINTESTINAL HEMORRHAGES

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AND

S. C. FRANCO, M.D.

BROOKLYN

Gastrointestinal hemorrhage from esophageal polyps is exceedingly rare. We wish to present the case of a girl who suffered repeated gastrointestinal hemorrhages over a period of five years. The bleeding was originally attributed to esophageal varices, but subsequent clinical study revealed multiple polyps of the esophagus as the cause of hemorrhage. These polyps were successfully removed by fulguration, which rendered the esophagus practically normal, and the patient has been free from hemorrhage since this procedure.

REPORT OF CASE

The patient, a girl of 10, was first admitted to the pediatric ward in the service of Dr. Charles Weymuller on July 27, 1935 and discharged on November 3. Her illness dated back to 1928, at which time jaundice, abdominal distention and engorgement of the veins of the abdominal wall were said to have been present. Blood was noted in the stool at that time. The first episode lasted several months, after which the patient felt entirely well until May 10, 1935. At this time pallor and jaundice were noted, and blood was once again present in the stool. The episode was transient, and the patient was well until the day of admission, when she complained of dizziness and vomited about half a glass of bright red blood. This was preceded by vague epigastric pain, which disappeared after the hematemesis.

The only other illnesses in the patient's past history were measles and otitis media.

On examination the patient appeared well nourished but weak and pale. There were two decayed teeth. The lungs were normal. The heart was not enlarged; the sounds were of fair quality, and no murmurs were heard. The abdomen was soft and not distended. There was no tenderness. The spleen was enlarged, firm and smooth and was not tender. It was felt 5 fingerbreadths below the costal margin. The liver could not be palpated. The extremities were normal.

The red cell count was 3,200,000 and the hemoglobin concentration 58 per cent. The white cell count was 13,600. A differential count showed 87 per cent polymorphonuclear neutrophils and 12 per cent lymphocytes. There were no abnormal

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cells. The platelet count was 262,500. The percentage of reticulocytes was 1. The urine was normal. The stool was grossly bloody, and clots were present. The stool remained bloody as late as July 31, and by this date the hemoglobin concentration had fallen to 25 per cent and the red cell count to 1,500,000. The white cell count was 62,000, and the differential count was normal. The level of urea nitrogen in the blood was 24.9 mg. per hundred cubic centimeters, and the levels of calcium, phosphorus and sugar were not significantly altered. The icterus index was 4. Blood continued to be present in the stool and on July 31 a direct transfusion of 150 cc. of blood was given. No improvement was noted,

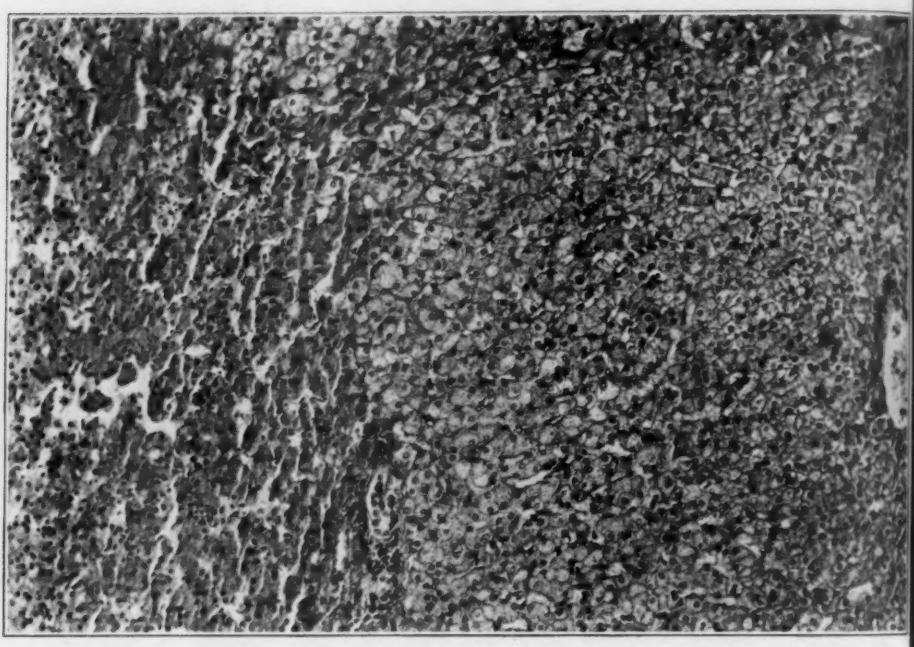

Fig. 1.—A section of a biopsy specimen taken from the liver.

and by August 2, air hunger was present and the patient was restless and prostrated. A soft blowing systolic murmur was heard at the apex. The spleen was still palpable. Dulness was noted in both flanks, and a fluid wave was present. Another transfusion of 150 cc. was given. By August 7, a week later, gross blood was no longer visible in the stool, but occult blood was still present. The physical findings associated with the presence of abdominal fluid were still in evidence.

The patient was placed on liver and iron therapy. By August 19 her condition had improved considerably. The spleen was still palpable, but the signs of ascites were less marked. The hemoglobin concentration was 51 per cent and the red cell count 2,600,000. The stool still contained occult blood. Steady improvement continued, and by September 9 the hemoglobin concentration had risen to 75

per cent and the red cell count to 3,620,000. The white cell count was 3,600 and had ranged between 3,000 and 4,500 for about two weeks. Occult blood was still present in the stool.

The diagnosis at this time was considered to be Banti's syndrome and hemorrhage from esophageal varices. The patient's condition was then good enough to warrant operation, and this was done on September 19. A left upper rectus incision was made, and the spleen, which was fixed by numerous fibrous adhesions to the surrounding tissues, was removed. It was stated in the report of the operation that the adhesions were old but moderately vascular. Two small

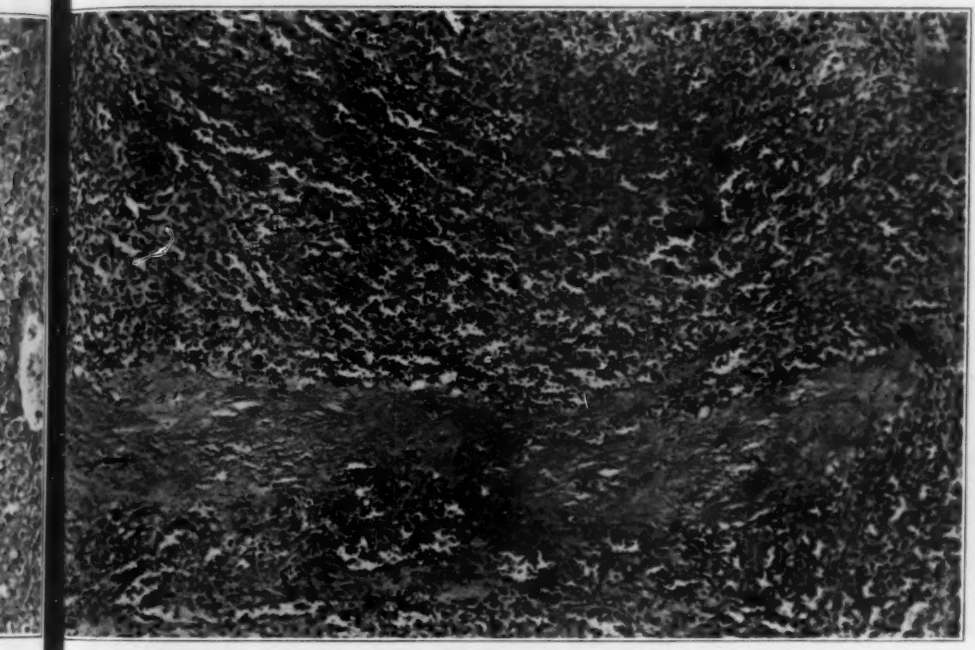

Fig. 2.—A section of the spleen.

accessory spleens measuring about 1 cm. in diameter were also removed. No abdominal fluid was found. The liver appeared grossly normal. A biopsy specimen was taken, however. Microscopic study of this specimen (fig. 1) showed distortion of structure, cellular infiltration around the smaller ducts and degeneration of many liver cells. The spleen (fig. 2) showed a general thickening of the fine reticulum and also of the larger trabeculae. There was a mild to moderate degree of periarterial fibrosis, and the sinuses were distinctly enlarged.

The patient's postoperative course was uneventful. The stool was first reported as giving a negative reaction for occult blood on September 28, nine days after operation. On October 1 the patient passed about 8 cc. of dark brown urine, which on microscopic examination was seen to be filled with red and with white

blood cells. At this time the patient noticed lumbar pain on the right side which became severe and radiated to the right loin. There was marked tenderness to pressure over the entire region of the right kidney. By October 5, the pain had disappeared and no more red cells were seen in the urine, though white cells were present for a few days more. By October 11, the patient was asymptomatic and the urine was clear. From this time on no untoward incidents occurred, and on discharge on November 3, 1935, the red cell count was 4,970,000, the hemoglobin concentration 78 per cent and the white cell count 11,000. The differential count was still normal, as it had been throughout the patient's hospitalization, though a shift to the left had been noted at times. No abnormal cells were seen at any time. The clotting time, the results of the fragility test and the bleeding time were all within normal range. The diagnoses at the time of discharge were (1) Banti's syndrome, (2) splenectomy and (3) right renal infarct.

The patient was admitted for the second time on May 19, 1937 and discharged on June 10. She was well until the night before entry, when vague epigastric distress developed and she felt nauseated. An enema given at this time yielded some tarry feces. Two hours after the enema, the patient had a bowel movement, and the stool was described as tarry. She rapidly became weak and was brought to the hospital the following morning. On examination the patient appeared anemic. A systolic murmur was heard at the apex and at the pulmonary area. The abdomen was not distended or tender. There was no ascites or venous engorgement. The liver and the kidneys could not be felt. Rectal examination showed nothing of note, though some tarry fecal material was seen on the glove.

The red cell count was 3,340,000 and the hemoglobin concentration was 52 per cent. The white cell count was 16,400. The differential count was normal. A tourniquet test showed no evidence of increased capillary fragility. The clot retraction time was four hours. The stool remained tarry until May 21, and on this date, the hemoglobin concentration was as low as 44 per cent and the red cell count 2,950,000. A brown stool was first noted on May 23. The patient improved progressively, and on June 4, the hemoglobin concentration was 61 per cent and the red cell count was 4,500,000. An esophagram was made on June 8; a fairly large constant defect measuring 2 by 1 cm. was noted in the distal portion of the esophagus. There were some irregularities in the anterior and the posterior portion of the lower part of the esophagus suggesting smaller varices (fig. 2). The patient was discharged on June 10, with the diagnoses of Banti's syndrome and hemorrhage from an esophageal varix.

The child was symptom free until the night of Jan. 29, 1938, when severe cramplike pain suddenly developed in the left lower quadrant of the abdomen. On the morning of January 30 she suddenly became nauseated and vomited about two glasses of bright red blood containing many clots. She was immediately brought to the hospital. The patient appeared listless and pale. The physical examination failed to reveal anything different from the results of previous physical examinations. Marked secondary anemia was again present; the red cell count was 1,580,000, and the hemoglobin concentration, 26 per cent. The white cell count was 26,000, and the differential count showed a shift to the left, with 84 per cent neutrophils. The blood urea nitrogen was 20.2 mg. per hundred cubic centimeters. The patient gradually improved on supportive therapy, and blood disappeared from the stool. A transfusion of 400 cc. of blood was given on February 1. A picture of the abdominal wall taken at this same time under infra-red rays showed no evidence of increased venous circulation. A roentgenogram of the chest

showed nothing abnormal, and barium sulfate studies of the esophagus once again revealed irregularities which were interpreted as varices.

Due to the patient's repeated episodes of hematemesis it was decided to operate once again in an attempt to prevent further esophageal hemorrhages by ligation of the coronary vein. On March 9 an exploration was performed by Dr. E. Goetsch through a right upper rectus incision. The peritoneum was opened without difficulty, and then numerous adhesions were encountered in the peritoneal cavity. The adhesions were so abundant that the abdominal viscera to the left of the midline could not be visualized. An attempt was made to visualize the stomach, but after only one third of the lesser curvature was exposed the procedure was abandoned because of the numerous vascular adhesions. The liver was noted to be slightly enlarged

Fig. 3.—A roentgenogram of the barium-filled esophagus, demonstrating translucent areas in the lower portion.

and somewhat soft. A biopsy specimen was taken and on microscopic examination showed mild degeneration. It was decided to do an omentopexy. The omentum was freed. A small incision was made in the peritoneum and the posterior rectus sheath, and the omentum was then brought through this incision and placed beneath the rectus muscle. It was felt that the absence of free fluid, the rather normal appearance of the liver and the absence of dilated veins were not consistent with the diagnosis of Banti's syndrome. The patient's postoperative course was uneventful, and she was discharged on March 23, 1938. The final opinion was undiagnosed disease and hemorrhage from an unknown cause.

The patient's next admission was on Aug. 28, 1939, on which day severe cramplike pain developed in the right lower quadrant of the abdomen associated

with nausea. There was no vomiting. The abdomen was somewhat distended. The percussion note was tympanitic, and borborygmus was present. There was no spasm, but tenderness was present just below and to the right of the umbilicus on moderate pressure. The red cell count was 5,100,000 and the hemoglobin concentration 99 per cent. The white cell count was 23,600. There was a shift to the left, with 86 per cent neutrophils. No abnormal cells were seen. A flat plate of the abdomen revealed nothing abnormal. It was thought that the patient might have either intestinal obstruction or acute appendicitis. The pain, however, subsided rapidly, and operation was withheld. Suddenly on September 3 the patient cried out and became unconscious. Her skin was pale and cold and clammy. The pulse was barely perceptible, and the rate was 130 per minute. The blood pressure was 70 systolic and 30 diastolic. Consciousness returned in a few minutes, and the patient was unable to say why she cried out. Examination revealed nothing of note. However, about one-half hour after returning to consciousness, the patient vomited nearly 5 fluidounces (150 cc.) of bright red blood. She was given supportive therapy, and one transfusion of 300 cc. of blood. She improved gradually, and the stool gave a negative reaction to the benzidene test on September 16. She was discharged on September 17.

The patient had to be readmitted on Jan. 27, 1940 for pain in the right lower quadrant of the abdomen similar to that occurring on her preceding admission. Examination of the abdomen revealed only moderate tenderness in the right lower quadrant. While in the hospital she had several similar bouts of pain, all of which subsided rapidly. She was discharged on February 4, with a final diagnosis of abdominal pain of unknown cause.

The patient's sixth admission to the hospital was on February 28. Two days prior to this, she had again had cramplike abdominal pain, and on the night of admission she vomited about 1 pint (470 cc.) of bright red blood. Shortly after admission she again vomited about 1 pint of blood. She was in shock. The blood pressure was 70 systolic and 50 diastolic, and the pulse rate was 116 per minute. The abdomen was soft and not distended. There were no masses or tenderness. The liver and the kidneys could not be palpated. The hemoglobin concentration was 49 per cent, and the red cell count was 3,400,000. The stool was tarry and gave a positive reaction for blood. Hepatic function tests yielded normal results, including the hippuric acid test, the galactose tolerance test and a dye excretion test. The patient's improvement was gradual, and no untoward incidents occurred. Barium sulfate studies of the esophagus once again revealed the irregularities previously described. Gastrointestinal roentgenograms and a barium sulfate enema showed nothing abnormal. It was decided to perform an esophagoscopic examination, and if varices were present it was planned to have them sclerosed by the method described by Moersch.[1] Esophagoscopy was performed for the first time on May 20, by Dr. R. L. Moorhead, and numerous pale, glistening projections of irregular size and shape were seen studding the surface of the mucosa. These were most numerous in the lower third of the esophagus. Some of these projections were sufficiently large to occlude the lumen. It was the opinion of the operator that these masses were polyps. Esophagoscopy was again done on June 6, and a biopsy specimen was taken. No sooner had the specimen been taken than there was a huge gush

1. Moersch, H. J.: Treatment of Esophageal Varices by Injection, Proc. Staff Meet., Mayo Clin. **15**:177 (March 20) 1940.

of dark venous blood, and within a few minutes the patient lost approximately 1,500 cc. of blood. The patient's pulse rose with great rapidity and soon became imperceptible, while the blood pressure dropped until it was unobtainable. Respirations became irregular, and the patient's condition was grave. Emergency measures were instituted. Epinephrine was given. The esophagus was packed with gauze from the cardia to the mouth. An infusion of physiologic solution of sodium chloride was begun while blood was obtained, and 500 cc. of blood was given before the patient left the operating room. The patient was heavily narcotized and treated with two further transfusions of 500 cc. each. Nothing was given by

Fig. 4.—A section of the biopsy specimen taken from an esophageal polyp. Note the blood spaces in the squamous epithelium.

mouth. Her condition improved rapidly, and by June 8, she was able to take fluids. On June 10, esophagoscopic examination was again performed. No evidence of bleeding was noted, and the sponges which had been used to pack the length of the esophagus could not be seen. The report of the histologic picture of the biopsy specimen, by Dr. J. N. Pierce, was as follows (fig. 4): "Gross description: The specimen consists of a small fragment of friable, wrinkled, membranous tissue less than 1 cm. in size. Microscopic description: In one small area approximately two low power fields in size the squamous epithelium lining the esophagus is thickened to three to four times its normal width. In the epithelium there are thin-walled endothelium-lined spaces distended with blood and accom-

panied by a delicate fibrous stroma. There is no penetration of the underlying tissue by the epithelium, and the basement membrane is intact." Dr. Pierce stated that he could not make a diagnosis of polyp from the specimen itself and that we would have to depend on the gross appearance at esophagoscopy. The esophagoscopists were reluctant to secure any more tissue for biopsy after the first severe hemorrhage. The decision was made, though not without trepidation, to fulgurate as many of the polyps as possible. Thereafter, the patient was

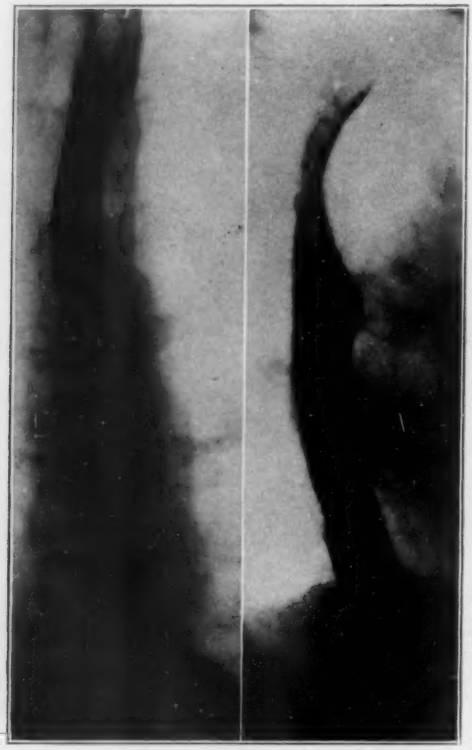

Fig. 5.—The esophagus after fulguration of the polyps, appearing almost normal.

operated on sixteen times by Dr. Moorhead and his staff, and the growths were gradually fulgurated from the upper portion of the esophagus to the cardiac end of the stomach. At the time of discharge on November 22, there was little or no evidence of polyposis.

The patient has remained perfectly well, and in June 1941 esophagoscopy revealed a somewhat dilated and tortuous tract with only three or four growths, 2 to 3 mm. in size. The esophagram was mainly normal and showed a few translucent areas (fig. 5).

COMMENT

In this patient the recurrent gastrointestinal hemorrhages were due to multiple polyps of the esophagus. The main proof of this pathologic situation rests on the repeated esophagoscopic examinations. The specimen of esophageal tissue secured for biopsy is small and does not reveal a real polyp. The outstanding finding in the microscopic section is the presence of blood vessels in the mucosa itself. Esophageal varices are ruled out by the esophagoscopic description of the polyps, the lack of portal hypertension and the absence of cirrhosis of the liver. The original splenomegaly is hard to explain satisfactorily. Its microscopic appearance is not characteristic of any special disease condition. It may have resulted from the hepatitis occurring in early childhood. Cirrhosis of the liver is ruled out by the absence of hepatic damage and the lack of evidence of portal hypertension either clinically or at operation. Thompson [2] and the members of the Spleen Clinic at Presbyterian Hospital, New York, have shown that congestive splenomegaly does occur in some children without cirrhosis of the liver and is due to stenosis of the portal vein from a congenital defect. In this group hemorrhage occurs from ruptured esophageal varices despite splenectomy. But in rare instances the stenosis may involve the splenic vein alone, and the patient may be cured by splenectomy. From the description of the operation, this does not seem to have been the situation in this patient.

Multiple polyps of the esophagus are rare, and in only 1 case in the literature, to our knowledge, has this condition been complicated by hemorrhages. In 1931 Ginsburg [3] reviewed this subject. He reported a case of his own and described a case reported by Patterson and another reported by Kernan. Hunt [4] reported a case of multiple polyps of the esophagus in 1937. In all these cases the patients complained of dysphagia, and in none of them was the disorder complicated by hemorrhage.

Even in the reported cases of solitary hemangioma [5] of the esophagus the condition has not been complicated by hemorrhage. In 1922 Timbal [6] described a case of multiple polyps of the esophagus in which the patient

2. Thompson, W. P.: The Pathogenesis of Banti's Disease, Ann. Int. Med. **14**:255 (Aug.) 1940.

3. Ginsburg, L.: Multiple Papillomas of Esophagus: Report of Case, Arch. Otolaryng. **14**:570 (Nov.) 1931.

4. Hunt, W. M.: Multiple Papilloma of Esophagus: Case Report, Ann. Otol., Rhin. & Laryng. **46**:752 (Sept.) 1937.

5. Vinson, P. P.; Moore, A. B., and Bowing, H. H.: Hemangioma of the Esophagus: Report of a Case, Am. J. M. Sc. **172**:416 (Sept.) 1926. Broders, A. C.; Vinson, P. P., and Davis, P. L.: Hemangio-Endothelioma of Esophagus: Report of Case, Arch. Otolaryng. **18**:168 (Aug.) 1933.

6. Timbal, L.: Tumeurs multiples de l'œsophage, Arch. d. mal. de l'app. digestif **12**:126, 1922.

suffered hemorrhages as a complication. According to this report, dysphagia developed in a young man aged 25 and several months later he suffered a severe hemorrhage from the esophagus. Subsequent roentgen and esophagoscopic investigation revealed a polyp in the upper portion of the esophagus and another one in the cardiac portion. The patient spontaneously expelled the upper polyp in a vomiting spell. Severe necrosis in the specimen prevented a definite microscopic diagnosis, but the findings were suggestive of a sarcomatous polyp. The polyp at the cardiac end of the esophagus progressed rapidly in size and finally produced such severe obstruction that a gastrostomy was necessary. Hemorrhages from the polyp recurred, and the patient died of hypostatic pneumonia. An autopsy was not performed. From the rather rapid clinical course and from comparison of the specimen with laryngeal pedunculated tumors, the author concluded that the patient had suffered from sarcomatous polyps of the esophagus.

Instances of multiple tumors of the gastrointestinal tract, complicated at times by hemorrhage, were reported by Bennecke [7] in 1906. He described numerous submucous cavernomas in the gastrointestinal tract of a man aged 52 who died of meningitis. The intestine from the duodenum to the rectum showed numerous nodules varying from pinhead to large bean size. They looked like varicose enlargements. The esophagus and the stomach had similar nodules. They were submucous in location, and while they were less numerous than in the intestine, they were larger. Microscopic examination demonstrated that the condition was due to enlargement of the submucous veins similar to the congenital deformity noted in cavernoma of the liver. Bennecke called the condition cavernous phlebectasia. He stated that 20 cases of similar abnormality had been described in the literature, and while in most of them the condition was asymptomatic, he referred to a report describing fatal internal hemorrhage in 2 children suffering from the condition.

The differentiation of esophageal polyps from esophageal varices by roentgen study of the esophagus after the instillation of barium sulfate is difficult. Buckstein [8] stated:

> The essential finding in the roentgen demonstration of esophageal varices is therefore the presence of rounded translucent areas, bead-like in appearance and involving usually the distal portion of the esophagus. There may be momentary variation in the appearance of these areas primarily as a result of peristaltic activity.

Polyps also appear as translucent areas in the lumen of the esophagus on roentgen study after the instillation of barium sulfate, and they are

7. Bennecke, H.: Ueber kavernöse Phlebektasien des Verdauungstraktus, Virchows Arch. f. path. Anat. **184**:171, 1906.

8. Buckstein, J.: Clinical Roentgenology of the Alimentary Tract, Philadelphia, W. B. Saunders Company, 1940, p. 60.

more prominent in the lower portion of the esophagus. No variation in the appearance of the translucent areas in the different roentgenograms was noted in the esophageal roentgen studies of the polyps in our case. This might be used as a point in the differential diagnosis of esophageal polyps and esophageal varices by roentgen study.

SUMMARY

A case is reported of massive recurrent hematemesis of five years' duration in a girl of 15. The condition apparently began as hepatitis with splenomegaly and was temporarily controlled by splenectomy. Although the liver showed no evidence of permanent damage and there was no increase in portal pressure, the hemorrhages recurred. Esophagoscopy ultimately revealed the presence of multiple polyps, which were removed by fulguration, with the recovery of the patient.

The small specimen obtained for biopsy, the taking of which was complicated by a severe hemorrhage, was unusual in that it presented numerous blood spaces in the thickened squamous epithelium.

In a review of the literature there was found but 1 other instance of hematemesis due to esophageal polyps.

Progress in Internal Medicine

INFECTIOUS DISEASES

A REVIEW OF SIGNIFICANT PUBLICATIONS IN 1941-1942

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The disruptive effects of the war on scientific study will soon be evident in the amount, quality and character of contributions dealing with infectious disease. Far-reaching changes in viewpoint and interests are also bound to occur incident to the transportation of troops to remote places of the earth, each with their special variety of infections in addition to the usual ones. Medical officers going to tropical regions will be obliged to familiarize themselves with infectious diseases which occur more commonly there, such as malaria, the dysenteries, yellow fever, dengue, cholera, melioidosis, protozoal and metazoal diseases, and the discomforts and dangers of various insect bites. Likewise, numerous other diseases will be encountered, particularly smallpox, tetanus, plague, typhus fever, kala-azar and relapsing fever, most of which the average physician in the United States has never seen.

Physicians who remain at home will have to learn to recognize and treat many of these infections in returned troops who have them either in active or in chronic form or who may be healthy carriers in whom the disease may develop or relapse after months or years of latency. In any event, it may be predicted that interest in exotic diseases will increase and many more contributions concerning them will begin to appear in the literature.

Aside from the exotic infections, epidemics of influenza, meningitis, typhus, dysentery, typhoid, the acute exanthems, mumps, venereal diseases and other infections will no doubt occur among large troop concentrations and especially among civilian populations harassed by poverty, vermin, hardship and starvation. Typhus is indeed already active in many parts of Europe, especially in the endemic centers in southeastern Europe and Spain and even in Germany among Russian prisoners of war.

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CHEMOTHERAPY

Chemotherapy with sulfanilamide and various derivatives was again the subject of many papers published during the year. No strikingly new facts or changes in opinion are evident, but it seems that the usual wave of overenthusiasm incident to the use of new remedies has passed and that the stage of realism has arrived. Numerous controlled studies have confirmed the value of some of the compounds in treating diseases like pneumococcic pneumonia, which need not be reviewed here; others leave the value of chemotherapy of certain infections doubtful, and still others report no beneficial effects at all in the treatment of the diseases studied.

Pneumococcic Empyema.—A summary [1] of recent publications shows that the incidence of empyema after pneumococcic lobar pneumonia has been reduced from 5 to about 1 per cent since the advent of therapy with sulfanilamide and various derivatives. Although the incidence is less, when empyema does occur after pneumonia in which treatment is with this type of compound it is apt to be atypical and more difficult to cure. Once the pneumonia has been controlled, such therapy should be discontinued even when pus has accumulated, since continued therapy is useless. Surgical drainage is necessary.

Subacute Bacterial Endocarditis.—Almost all reports on this disease reflect pessimism over the results obtained with the chemotherapeutic methods used at present. Willius,[2] for example, finds but little convincing evidence to increase one's optimism. Many reported cures he believes occurred in cases of doubtful or unproved disease. Similar views are expressed by Kinsella.[3] An example of the confusion in bacteriologic diagnosis which may arise is illustrated in one report [4] of a cure supposedly obtained in a patient whose infection was most likely caused by, or associated with, alpha hemolytic streptococci, not with Streptococcus viridans.[5]

Poston and Orgain [6] studied the bacteriostatic effect of sulfanilamide and various derivatives on twenty-five strains of Str. viridans. The

1. Burford, T. H., and Blades, B.: The Influence of Sulfonamide Therapy on Postpneumonic Empyema Thoracis, J. A. M. A. **118**:950-952 (March 21) 1942.

2. Willius, F. A.: Cardiac Clinics: A Talk on the Hapless Therapy of Subacute Bacterial Endocarditis, Proc. Staff Meet., Mayo Clin. **17**:216-218 (April 8) 1942.

3. Kinsella, R. A.: Chemotherapy of Bacterial Endocarditis, Ann. Int. Med. **15**:982-986 (Dec.) 1941.

4. Moore, G. B., and Tannenbaum, A. J.: Streptococcus Viridans Septicemia: A Cure with Sulfapyridine, J. A. M. A. **118**:372-373 (Jan. 31) 1942.

5. Nye, R. N.: Streptococcus Viridans Septicemia, Correspondence, J. A. M. A. **118**:917 (May 14) 1942.

6. Poston, M. A., and Orgain, E. S.: Comparison of the Bacteriostatic Effect of the Sulfonamide Drugs upon the Growth of Twenty-Five Strains of Streptococcus Viridans, Am. J. M. Sc. **203**:577-580 (April) 1942.

growth of most strains was inhibited by the drugs in vitro; that of three was inhibited to a considerable extent, and seven strains were not affected at all. The study indicates that different strains vary greatly in their susceptibility to the compounds used.

A few clinicians still advocate further trial with combination therapy using heparin and sulfanilamide or one of its derivatives,[7] but others [8] feel that heparin should no longer be used according to the technic originally advised. General opinion [9] seems to favor further experimental therapy with sulfanilamide and its derivatives now in use and continuation of the trial of newly synthesized compounds in the hope that an efficient one will be found.

Osgood [9a] reports favorable results in the treatment of subacute bacterial endocarditis with neoarsphenamine.

Staphylococcic Infections.—Torrey, Julianelle and McNamee [10] question the high degree of success reported by others in the chemotherapy of staphylococcic septicemia. In many cases of "cure" it is possible that staphylococci were transient and innocuous in the circulation. While in certain cases chemotherapy may be helpful in controlling the infection, it is not, the authors believe, strikingly helpful in the majority of cases of genuine staphylococcic septicemia. In their own series of cases, in which treatment was with sulfanilamide and some of its derivatives, the mortality rate was 67 per cent, or about the same as in many previously reported cases in which such compounds were not used.

In treating staphylococcic osteomyelitis Hoyt and his associates [11] obtained better results with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) therapy alone than with surgical treatment in addition.

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7. Leech, C. E.; Faulkner, J. M.; Duncan, C. N.; McGinn, S.; Porter, R. R., and White, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis: Further Experiences, J. A. M. A. **117**:1345-1350 (Oct. 18) 1941.

8. MacLean, J.; Meyer, B. B. M., and Griffith, J. B.: Heparin in Subacute Bacterial Endocarditis: Report of Case and Critical Review of Situation, J. A. M. A. **117**:1870-1875 (Nov. 29) 1941.

9. Heyer, H. E., and Hick, F. K.: Experiences in the Treatment of Subacute Bacterial Endocarditis with Sulfanilamide, Sulfapyridine, and Sulfathiazole: A Review of Previously Reported Treated Cases Including One Cure and One Aborted Case, Ann. Int. Med. **15**:291-303 (Aug.) 1941. Field, H.; Hoobler, S. W., and Avery, N. L.: Results of Chemotherapy in Subacute Bacterial Endocarditis, Am. J. M. Sc. **302**:798-803 (Dec.) 1941.

9a. Osgood, E. E.: Neoarsphenamine Therapy of Bacterial Infections with a Method of Administration to Maintain Uniform Blood Levels for the Treatment of Serious Staphylococcic Infections and Subacute Bacterial Endocarditis, Arch. Int. Med. **69**:746-763 (May) 1942.

10. Torrey, R. G.; Julianelle, L. A., and McNamee, H. G.: The Sulfonamide Therapy of Staphylococcal Septicemia, Ann. Int. Med. **15**:431-445 (Sept.) 1941.

11. Hoyt, W. A.; Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcic Osteomyelitis: Treatment with Sulfathiazole Without Operation, J. A. M. A. **117**:2043-2049 (Dec. 13) 1941.

They cite the dissenting opinion of Melton,[12] who states that sulfathiazole in his experience did not lessen the need for surgical intervention or check the progress of suppuration. Melton[13] also is unenthusiastic about the effects of the drug in the treatment of staphylococcic pulmonary infections. Sulfathiazole failed to cause a significant response in 3 of 4 cases, yet the patient recovered in each case.

Michael[14] reports 5 cases of staphylococcic pneumonia following infection with influenza A virus. In 4 cases treatment was with sulfathiazole, and in 1 case the patient died. The author believes that sulfathiazole is indicated in the treatment, but a perusal of evidence given in his charts is not convincing. In 2 cases the drug was given in large doses for six days, without influence on the course of the disease. In both cases, the drug was stopped and improvement occurred later. In 1933 I reported 6 cases of staphylococcic pneumonia, with recovery in 4 without chemotherapy. Thus far too few cases have been studied with sufficient control to assure one of the value of treatment with sulfanilamide derivatives.

From experimental studies Kolmer and Brown[15] conclude that the results of chemotherapy of staphylococcic infections are still unsatisfactory as compared with the effects obtained in infections caused by hemolytic streptococci or by pneumococci.

Meningitis.—The chemotherapy of meningitis caused by meningococci, hemolytic streptococci, pneumococci, influenza bacilli, staphylococci and other organisms has been so recently reviewed by Finland and Dingle[16] that further comment is unnecessary here. They point out the beneficial effects of such treatment obtained in most cases of infection caused by these bacteria. They show, however, the disappointing truth that the curative effects of chemotherapy of pneumococcic meningitis are not as good as many reports seem to indicate. The present mortality rate in cases in which chemotherapy is employed is nearer to 80 per cent than 35 per cent, as previously claimed.

Scarlet Fever.—Top and Young[17] found but little difference in the results of treatment of scarlet fever with sulfanilamide, convalescent

12. Melton, G.: Sulfathiazole in Treatment of Staphylococcal Infections, Lancet **1**:274-278 (March 1) 1941.

13. Melton, G.: Sulphathiazole in Staphylococcal Lung Infection, Lancet **2**: 522-523 (Nov. 1) 1941.

14. Michael, M.: Staphylococcus Aureus Pneumonia, with Special Reference to Its Occurrence as a Complication of Influenza, J. A. M. A. **118**:869-874 (March 14) 1942.

15. Kolmer, J. A., and Brown, H.: Chemotherapy and Chemoserotherapy of Staphylococcic Infections, Arch. Int. Med. **69**:636-646 (April) 1942.

16. Finland, M., and Dingle, J. H.: Treatment of Meningitis, New England J. Med. **225**:825-832 (Nov. 20) 1941.

(Footnotes continued on next page)

serum or antitoxin. Both serum and antitoxin gave slightly better results than sulfanilamide.

Rheumatic Fever.—In opposition to two previous favorable reports Stowell and Button [18] do not recommend the use of small doses of sulfanilamide given over long periods to prevent infections with hemolytic streptococci, which so often precede an attack of rheumatic fever. In about half the children they treated signs of toxicity developed. To be of consistent value the drug would have to be given annually during the winter months until the patient is 17 or 18 years of age.

Hopkins [18a] failed to obtain any beneficial effects in the treatment with sulfanilamide or sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) of 12 patients with rheumatic fever and 49 with streptococcic tonsillitis. Streptococcic tonsillitis developed in 2 patients undergoing intensive treatment with sulfapyridine.

Bacillary Dysentery and Typhoid Fever.—Favorable reports continue to appear on the treatment with sulfaguanidine (sulfanilylguanidine) of patients with acute bacillary dysentery and of carriers of dysentery bacilli. Anderson and Cruickshank [19] report good clinical results and a diminution of the convalescent carrier rate. Hardy and his associates [20] had excellent results in the treatment of infection caused by the Flexner, the Newcastle and the Shiga type of bacillus. The carrier state seldom exceeded five days. Sulfaguanidine, contrary to other previous and less favorable reports, proved of value in ridding carriers of the bacilli and may serve as an important epidemiologic measure in this respect. Rantz and Kirby [21] rid 9 of 11 carriers of bacilli, and in the 2 instances of failure the organisms were not typical Flexner bacilli. In one study [22] on chil-

17. Top, F. H., and Young, D. C.: The Treatment of Moderately Severe Scarlet Fever: A Study of Alternate Patients Treated with Sulfanilamide, Convalescent Serum and Scarlet Fever Antitoxin, J. A. M. A. **117**:2056-2060 (Dec. 13) 1941.

18. Stowell, D. D., and Button, W. N.: Observations on the Prophylactic Use of Sulfanilamide on Rheumatic Patients with Report of One Death, J. A. M. A. **117**:2164-2166 (Dec. 20) 1941.

18a. Hopkins, W. A.: Use of Sulfonamide Group of Drugs in Treatment of Tonsillitis Due to Beta Hemolytic Streptococcus and in Acute Rheumatic Fever, Ann. Rheumatic Dis. **2**:233-247 (Dec.) 1941.

19. Anderson, D. E. W., and Cruickshank, R.: Treatment of Bacillary (Flexner) Dysentery with Sulfanilylguanidine, Brit. M. J. **2**:497-500 (Oct. 11) 1941.

20. Hardy, A. V.; Watt, J., and Peterson, J.: Studies of the Acute Diarrheal Diseases: VIII. Sulfaguanidine in the Control of Shigella Dysenteriae Infections, Pub. Health Rep. **57**:529-535 (April 10) 1942.

21. Rantz, L. A., and Kirby, W. M. M.: Sulfaguanidine in the Treatment of Dysentery Carriers, J. A. M. A. **118**:1268-1271 (April 11) 1942.

22. Cooper, M. L.; Zucker, R. L., and Wagoner, S.: Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children, J. A. M. A. **118**:1520-1523 (Nov. 1) 1941.

dren with acute diarrheal disease sulfathiazole was used with success in treating those whose stools contained Flexner and Sonne dysentery bacilli but not in treating the rest. The drug was also effective in preventing the carrier state in convalescent patients.

Sulfaguanidine was used effectively in clearing a colony of mice of most carriers of an enzootic Salmonella infection.[23]

Hall [24] had no success in treating 20 patients with typhoid fever. Sulfaguanidine did not decrease the duration or the intensity of the disease or clear the stool of typhoid bacilli. The same number of complications occurred as in 20 untreated patients. Similar results were reported by Watt and Peterson.[24a] Cutting and Robson [25] state that there is no dependable or efficient curative drug for treating typhoid carriers. Six carriers studied by them were not cured by treatment with hydroxyphenothiazone (thionol), phenothiazine, soluble iodophthalein, sulfaguanidine or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). Cholecystectomy also fails in a considerable number of cases. Similar results were reported by another group of investigators.[26] Sulfaguanidine failed to eliminate typhoid bacilli from the stool in 5 carriers. Oral treatment with soluble iodophthalein in 65 cases in which typhoid bacilli were present in the bile rendered the bile sterile in 32 per cent but freed the stool from the bacilli in only 8 per cent.

Cholera.—According to Griffitts,[26a] sulfathiazole, sulfadiazine and sulfanilamide inhibited the growth of Vibrio cholerae in vitro. Sulfathiazole, sulfadiazine, succinylsulfathiazole and sulfaguanidine given intragastrically were effective in the treatment of mice experimentally infected with V. cholerae.

A group [27] from the Mayo Clinic gives an unenthusiastic report of sulfaguanidine treatment of various types of chronic ulcerative colitis

23. Beamer, P. R.: Sulfanilylguanidine in Control of Salmonella Infection and Carrier State in Mice, Proc. Soc. Exper. Biol. & Med. **49**:418-421 (March) 1942.

24. Hall, W. M.: Use of Sulfaguanidine in a Controlled Series of Typhoid Cases, New Orleans M. & S. J. **94**:283-284 (Dec.) 1941.

24a. Watt, J., and Peterson, J. S.: Sulfaguanidine Noneffective in the Treatment of Typhoid Fever and Typhoid Carriers, Pub. Health Rep. **57**:872-873 (June 5) 1942.

25. Cutting, W. C., and Robson, G. B.: The Alleged Efficiency of Medicinal Treatment of Typhoid Carriers, J. A. M. A. **118**:1447-1449 (April 25) 1942.

26. Saphir, W.; Baer, W. H., and Plotke, F.: The Typhoid Carrier Problem, J. A. M. A. **118**:964-967 (March 21) 1942.

26a. Griffitts, J. J.: Laboratory Studies of the Effect of Sulfonamide Drugs on V. Cholerae, Pub. Health Rep. **57**:814-818 (May 29) 1942.

27. Stickney, J. M.; Heilman, F. R.; Bargen, J. A., and Dearing, W. N.: Sulfaguanidine in Ulcerative Intestinal Disease, Proc. Staff Meet., Mayo Clin. **17**: 33-44 (Jan. 21) 1942.

not due to Endamoeba histolytica, Mycobacterium tuberculosis or the virus of lymphogranuloma venereum. While "many" patients apparently were helped by sulfaguanidine, the authors conclude that the place of the drug in the treatment of ulcerative intestinal disease has not been established but that its value in the therapy of some intestinal diseases "seems definite."

As may be expected, attempts are being made to synthesize a compound better than sulfaguanidine for the treatment of intestinal infections. In testing a number of drugs Poth and Knotts [28] found that succinylsulfanilamide and succinylsulfathiazole were effective experimentally. The latter drug was tested in a number of patients with various intestinal diseases. In 95 of 100 cases the intestinal flora, particularly of colon bacilli, was greatly altered.

Virus Diseases.—Sulfanilamide and some of its derivatives had no influence on experimental infection with vaccinia, smallpox [29] or western equine encephalomyelitis.[30] Although chemotherapy apparently prevented death of animals infected with the virus of lymphogranuloma venereum,[31] the effects were not always curative. Similar results were obtained by Rodaniche.[32] Chemotherapy influenced the disease in mice favorably, but the virus persisted in the brain. Because of the apparent effect of the drugs on the virus of lymphogranuloma venereum, Rake, Jones and Nigg [33] tested chemotherapeutic agents on the related viruses of mouse pneumonitis and meningopneumonitis. The effect of chemotherapy on the viruses of lymphogranuloma venereum and mouse pneumonitis, in addition to their apparent particulate nature, suggests to the authors that these infectious agents and also the one causing psittacosis are not true viruses.

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28. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, Arch. Surg. **44**:208-222 (Feb.) 1942.

29. Kolmer, J. A., and Brown, H.: Failure of Sulfanilamide in Treatment of Experimental Vaccinia Rabbits, Proc. Soc. Exper. Biol. & Med. **48**:138-140 (Oct.) 1941.

30. Schlatthauer, C. F.: Treatment of Equine Encephalomyelitis (Western) with Certain Sulfonamide Compounds: An Experimental Study, Proc. Staff Meet., Mayo Clin. **17**:187-189 (March 25) 1942.

31. Jones, H. P.; Rake, G., and McKee, C. M.: Chemotherapy of Lymphogranuloma Venereum with Sulfonamide Drugs, Proc. Soc. Exper. Biol. & Med. **48**:318-323 (Oct.) 1941.

32. Rodaniche, E. C.: Sulfanilylguanidine and Sulfanilamide in the Treatment of Lymphogranuloma Venereum Infection of Mice, J. Infect. Dis. **70**:58-61 (Jan.-Feb.) 1942.

33. Rake, G.; Jones, H., and Nigg, C.: Sulfonamide Chemotherapy of Mouse Pneumonitis, Meningopneumonitis and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **49**:449-452 (March) 1942.

Miscellaneous Infections.—In cases of filariasis[35] sulfapyridine controlled lymphadenitis which was probably caused by secondary streptococcic infection but had no effect on the filarias in the blood stream. Sulfadiazine had a beneficial effect in reducing the number of Haemophilus pertussis organisms in inoculated mice.[36] Hinshaw and Feldman[37] present further evidence of the favorable effect of sodium p, p' - diaminodiphenylsulfone - N, N' - didextrosesulfonate (promin) on experimental tuberculosis in guinea pigs. All of the untreated control animals died, while 84 per cent of 80 treated animals remained well. Coggeshall, Maier and Best[38] used this compound and sulfadiazine in the treatment of malaria in human beings caused by Plasmodium vivax and by Plasmodium falciparum and obtained definite curative effects in most cases. It appears, therefore, that compounds unrelated to quinine or atabrine may be valuable antimalarial agents, but they should at present only be regarded as substitutes and not used in preference to older drugs.

Sulfathiazole seemed to be of benefit in the treatment of 7 patients with infectious mononucleosis,[39] but the number tested is too small to convince one of its value.

Untoward Effects.—In discussing the advantages of any form of treatment it is always necessary to consider its harmful effects as well. A number of newly recognized untoward effects have been reported, some in experimental animals and others in patients. For example, sulfaguanidine caused extensive hyaline sclerosis and calcification of blood vessels in young rats.[40] In other experiments with rats the drug caused

34. Deleted by author.

35. Earle, K. V.: Sulfapyridine in Filariasis: Further Experiences, Lancet **2**: 667-668 (Nov. 29) 1941.

36. Hornibrook, J. W.: Sulfadiazine in Murine Pertussis, Pub. Health Rep. **57**:535-537 (April 10) 1942.

37. Hinshaw, H. C., and Feldman, W. A.: Treatment of Experimental Tuberculosis: Use of Sodium P, P'-Diaminophenylsulfone-N, N'-Didextrose Sulfonate ("Promin") with Notes on Some Toxic Effects Observed in Man, J. A. M. A. **117**:1066-1068 (Sept. 27) 1941.

38. Coggeshall, L. T.; Maier, J., and Best, C. A.: The Effectiveness of Two New Types of Chemotherapeutic Agents in Malaria, J. A. M. A. **117**:1077-1081 (Sept. 27) 1941.

39. Hoffman, H. T.; Lees, H. D., and Comroe, B. I.: Use of Sulfathiazole in Infectious Mononucleosis, Am. J. M. Sc. **203**:731-736 (May) 1942.

40. Daft, F. S.; Spicer, S. S., and Sebrell, W. H.: The Occurrence of Hyaline Sclerosis and Calcification of Blood Vessels in Rats on Sulfaguanidine, Pub. Health Rep. **57**:217-218 (Feb. 13) 1942.

hypertrophy and hyperemia of the thyroid.[41] French and Weller [42] noted interstitial myocarditis in patients in whom the sole common factor was the use of sulfanilamide compounds. Similar lesions were caused experimentally in animals.

In one study [43] while "drug-fever" developed in only 5 per cent of sulfathiazole-treated patients after the seventh day of therapy, 36 per cent had fever if the course of treatment was repeated and 80 per cent of those who had fever after the second course also had fever after a third course. The authors therefore justly advise the use of sulfathiazole for the more serious infections only.

Although recent experience in Hawaii in the treatment of war wounds with sulfanilamide or one of its derivatives was highly satisfactory, it must be remembered that in contrast with injuries received during trench warfare, these wounds were undoubtedly cleaner. No doubt local chemotherapy will be of value even in grossly contaminated wounds, but final evaluation is not yet possible. Bick [44] points out that sulfanilamide or sulfathiazole applied to wounds of soft tissue and to clean surgical incisions delays healing by about 50 per cent and promotes scarring. They must be used, nevertheless, in contaminated wounds and even when soiling is anticipated.

Taylor [45] advises against stuffing a "sulfonamide compound" into "every cavity, scratch, wound or orifice" on the grounds that "all sulfonamides in common use" are irritant drugs which at times may themselves cause abscess formation and peritoneal adhesions. The practice of using these chemicals in clean wounds, including appendectomy wounds, is questionable.

Drug Fastness.—According to certain experiments,[46] gonococci become sulfanilamide "fast" or sulfapyridine (*2*-[paraaminobenzenesulfonamido]-pyridine) "fast" relatively easily, but little, if any, tolerance for sulfathiazole develops in a test tube. In this respect the gonococcus seems to differ from the pneumococcus, which when it becomes drug fast to one compound is also drug fast to others.

41. Mackenzie, J. B.; Mackenzie, C. G., and McCollum, E. V.: The Effect of Sulfanilylguanidine on the Thyroid of the Rat, Science **94**:518-519 (Nov. 28) 1941.

42. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, Am. J. Path. **18**:109-118 (Jan.) 1942.

43. Lyons, R. H., and Balberor, H.: Febrile Reactions Accompanying the Readministration of Sulfathiazole, J. A. M. A. **118**:955-958 (March 21) 1942.

44. Bick, E. M.: Observations on the Topical Use of Sulfonamide Derivatives, J. A. M. A. **118**:511-513 (Feb. 14) 1942.

45. Taylor, F. W.: The Misuse of Sulfonamide Compounds, J. A. M. A. **118**: 959-961 (March 21) 1942.

46. Carpenter, C. M.; Charles, R., and Allison, S. D.: Effect of Gradually Increased Concentrations of Sulfathiazole on the Gonococcus in Vitro, Proc. Soc. Exper. Biol. & Med. **48**:476-478 (Nov.) 1941.

Resistance to sulfanilamide may also develop in hemolytic streptococci, according to the study of Hendry.[47] The acquired drug fastness of the strain studied was unchanged after fourteen subsequent passages in mice.

According to one group of workers,[48] sulfanilamide and various derivatives have no particular specificity in vitro for different bacteria. By using a special ratio involving paraaminobenzoic acid, each of the six compounds tested was equally effective in inhibiting growth of a variety of bacteria. The authors' views are supported by some observers who noted no particular difference in the effect of sulfapyridine, sulfathiazole or sulfadiazine in the treatment of pneumococcic pneumonia, except, of course, in the difference of the toxic effects of the drugs on patients.

COCCIC DISEASES

Pneumococcic Pneumonia.—O'Hara [49] calls attention, as I did in the annual review for 1940,[50] to the steady decline in the death rate of pneumonia since 1900. No specific antipneumococcic measures can be credited for this favorable trend, which is also present in mortality statistics of other infectious diseases. He believes, as I do, that the decline in mortality has been brought about by many complex factors, including better housing and better nutrition. It is interesting to speculate on the possible effect on the mortality curve had sulfanilamide derivatives been introduced fifteen or twenty years ago. The striking further reduction in mortality rate since 1938 can be unquestionably attributed for the most part to chemotherapy.

The results of a statistical study [51] indicate that the death rate from pneumonia in 1940 was about 10 per hundred thousand insurance policy holders. It is possible that this low rate may be near the minimum, below which it is unlikely that mortality can be reduced. Of the policy holders dying from pneumonia, 84 per cent had had chemotherapy, 73 per cent without additional serum and only 11 per cent with serum. Less than 1 per cent had received serum alone. Of the 464 cases of pneumonia in which bacteriologic study was done, infection was pneumococcic in origin in 72 per cent, streptococcic in 5.6 per cent and staphylo-

47. Hendry, J.: A Study of Hemolytic Streptococci from a Horse Treated with Sulfanilamide After Streptococcal Bacteremia Developed During Immunization, J. Infect. Dis. **70**:112-118 (March-April) 1942.

48. Wyss, O.; Grubaugh, K. K., and Schmelkes, F. C.: Non-Specificity of Sulfonamides, Proc. Soc. Exper. Biol. & Med. **49**:618-621 (April) 1942.

49. O'Hara, D.: Pneumonia in Massachusetts: 1900-1940, New England J. Med. **225**:402-404 (Sept. 11) 1941.

50. Reimann, H. A.: Infectious Diseases: A Review of Significant Publications in 1939-1940, Arch. Int. Med. **66**:478-525 (Aug.) 1940.

51. Some Current Results in Pneumonia Treatment, Statist. Bull. Metrop. Life Insur. Co. **22**:1-4 (Oct.) 1941.

coccic in 2.2 per cent; the causative organism was not identified in the others. In the series of cases studied apparently no attempt was made to type the pneumococcus supposedly involved in one fourth of the cases, against the advice of many authorities who properly urge that specific etiologic diagnoses still be made in all cases.

In reading papers one must not be misled by statements [52] apparently reflecting uncontrolled personal experience, such as "In the decade following the war, the pneumococcus could rarely be found" in pneumonia or "During the past decade, pneumococci again have been demonstrated with increasing frequency." Nor is there any evidence aside from increasing recognition that "the so-called virus type of pneumonia is increasing in frequency."

In studying the flora in the nasopharynx of children in an orphanage Smillie [53] found type XIV pneumococci to be present in 32 per cent, or ten times the usual expectancy, yet pneumonia did not develop in any of the children. This gives evidence that an invasive type of pneumococcus may be widespread without causing symptoms, unless, as later happened in some cases, mild infection of the respiratory tract makes invasion possible. Of 31 instances of pneumonia, 10 were caused by organisms of type XIV; of 83 patients with a "cold," 30 carried organisms of type XIV, and of 40 healthy children, 10 carried type XIV pneumococci in the throat. There was, therefore, no statistical significance to the prevalence of the pneumococcus in those sick or well in the group studied.

In a study [54] of the problem of types of pneumococci seventeen "new" types in addition to the thirty-two known ones were found. Many are subtypes of established types, but nine are distinctive in themselves. Few of the newly classified types have much virulence for mice.

Mørch,[54a] of Copenhagen, obtained Walter's new types from New York and reclassified them with his own numerical system. He added more new types and subtypes of his own, so that at present sixty-eight separate or slightly different types are included in the complicated pattern. One wonders if the end will ever be reached.

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52. Wood, H. G.: Present Day Treatment of Pneumonia, Minnesota Med. **25**:24-27 (Jan.) 1942.

53. Smillie, W. G.: The Epidemiology of Pneumonia: The Role of Type XVI Pneumonococci in Producing Illness, Tr. A. Am. Physicians **56**:129-138, 1941.

54. Walter, A. W.; Guevin, V. H.; Beattie, M. V.; Cotler, H. Y., and Bucca, H. B.: Extension of Separation of Types Among the Pneumococci: Description of Seventeen Types in Addition to Types 1 to 32 (Cooper) with Recommendation for Terminology of All Types Reported Through 1940, J. Immunol. **41**:279-294 (July) 1941.

54a. Mørch, E.: Further Studies on the Serology of the Pneumococcus Group, J. Immunol. **43**:177-202 (Feb.) 1942.

In extending previous observations Frisch and Price [55] report the value of examination of sputum as a reliable guide in prognosis and therapy in 270 cases. Sputum counts with pneumococci exceeding 50 per oil immersion field indicated potentially overwhelming infection. Chemotherapy was reserved for patients with 11 to 50 or more pneumococci per field, and those patients whose sputum had 10 or fewer organisms per field all recovered without therapy.

In Bigg's [56] experiments on dogs the injection of small amounts of specific soluble substance during experimental pneumococcic pneumonia resulted in overwhelming infection, apparently because of impaired phagocytosis in the pneumonic area and an inability to localize the infection. These experiments confirm earlier ones by Cole and by Robertson regarding the deleterious effect of the capsular substance in neutralizing specific immune bodies in cases of pneumococcic pneumonia.

According to Wooley and Sebrell,[57] mice fed a diet deficient in riboflavin or thiamine were more susceptible to fatal infection with pneumococci than mice fed a complete diet. The daily additional feeding of large amounts of both substances to mice kept on diets deficient in the respective vitamins at the time of inoculation did not reduce the number of animals dying from the infection.

Other Forms of Pneumonia.—Michael [14] reports cases of staphylococcic pneumonia, in many of which the pneumonia was preceded by an attack of influenza, which appeared to be an important predisposing factor. Other cases are reported by Gáspár.[58] A good review of pulmonary tularemia, or tularemic pneumonia, with a bibliography and a report of 3 fatal cases was made by Kennedy.[59] Julianelle [60] reviewed the subject of Bacillus Friedländer pneumonia. Two cases of pulmonary syphilis, or syphilitic pneumonia, were discussed by Lieu,[61] and the

55. Frisch, A. W., and Price, A. E.: Sputum Studies in Pneumonia: The Selection of Therapy, Ann. Int. Med. **15**:987-993 (Dec.) 1941.

56. Bigg, E.: Influence of Specific Soluble Substance on the Course of Experimental Pneumococcus Pneumonia, Proc. Soc. Exper. Biol. & Med. **48**:245-247 (Oct.) 1941.

57. Wooley, J. G., and Sebrell, W. H.: Nutritional Deficiency and Infection: I. Influence of Riboflavin or Thiamin Deficiency on Fatal Experimental Pneumococcal Infection in White Mice, Pub. Health Rep. **57**:149-161 (Jan.) 1942.

58. Gáspár, I. A.: Study of Primary Staphylococcic Pneumonias Occurring at the Rochester General Hospital, New York State J. Med. **41**:834-840 (April 15) 1941.

59. Kennedy, J. A.: Pulmonary Tularemia, J. A. M. A. **118**:781-787 (March 7) 1942.

60. Julianelle, L. A.: Pneumonia of Friedländer's Bacillus, Ann. Int. Med. **15**:190-206 (Aug.) 1941.

61. Lieu, V. T.: Acquired Pulmonary Syphilis: Report of Two Cases with Review of Literature, Chinese M. J., March 1940, supp. 3, pp. 145-157.

pertinent literature was reviewed. Hegglin [62] discussed cases of a peculiar form of infiltration of the lungs, or atypical pneumonia, with positive Wassermann reactions. Two cases of pulmonary histoplasmosis were presented by Meleney.[63]

Doubt has been cast on the existence of so-called "rheumatic pneumonia." Two authors [64] were unable to find Aschoff bodies in the lungs in 45 cases. There were many patches of dark red rubbery areas, but the lesions were composed of the results of vascular damage, as are rheumatic lesions elsewhere. Although the pathologic picture is characteristic, the authors do not believe it represents a specific pulmonary lesion. These conclusions are at variance with several previous publications and my own observations, according to which Aschoff bodies, or bodies closely resembling them, were present in the pulmonary lesions during rheumatic fever.

According to Wolman and Bayard,[65] the nature of the fatty substance in the lung in cases of oil aspiration pneumonia can be determined by the gross appearance of the lesion, by special staining reactions, by histologic changes and by fluorescence of the pulmonary lesion. Tables are included in the paper to assist identification.

"Virus" pneumonia is discussed on page 156.

Streptococci Infection.—Boisvert [66] points out how important it is to identify the type of hemolytic streptococcus causing disease in order to determine the source of an epidemic and to control it. In many cases he believes failure to determine the type by the Griffith slide-agglutination technic may be due to the prozone phenomenon, which may be overcome by diluting the typing serum sometimes as much as 1 : 80.

Rantz [67] reviews the literature on the typing of hemolytic streptococci of the Lancefield group A. There are no types especially responsible for scarlet fever. Types 1, 2, 3 and 4 are perhaps more frequent causes than other types. Even in a local epidemic several types may be prevalent, and as in the case of meningococci, the prevalence of certain types in a community changes from year to year. Hemolytic streptococci are often found in the throats of healthy persons, but their type fre-

62. Swiss Society for Internal Medicine, Foreign Letters (Switzerland), J. A. M. A. **117**:1111 (Sept. 27) 1941.

63. Meleney, H. E.: Pulmonary Histoplasmosis: Report of Two Cases, Am. Rev. Tuberc. **44**:240-247 (Aug.) 1941.

64. Epstein, E. L., and Greenspan, E. B.: Rheumatic Pneumonia, Arch. Int. Med. **68**:1074-1094 (Dec.) 1941.

65. Wolman, I. J., and Bayard, A. B.: Experimental Aspiration Pneumonia: Fluorescence and Pathology, Am. J. M. Sc. **202**:542-553 (Oct.) 1941.

66. Boisvert, P. L.: The Typing of Hemolytic Streptococci, Science **94**:193-194 (Aug. 22) 1941.

67. Rantz, L. A.: The Serological Typing of Hemolytic Streptococci of the Lancefield Group A, J. Clin. Investigation **21**:217-227 (March) 1942.

quency is not correlated with the types causing scarlet fever in the same season, and the same type may cause both scarlet fever and tonsillitis. According to various reports, however, the types causing scarlet fever and those causing surgical infections are often different, and postscarlatinal complications are usually caused by types other than those responsible for the scarlet fever. Nevertheless, according to Rantz's own studies, and as one would expect, the type distribution of strains from various sources is similar whether they cause otitis media or surgical infections or are from excised tonsils. All types appear to be similarly affected by sulfanilamide and various derivatives. By the use of his technic for typing, 80 to 95 per cent of strains could be classified.

Touroff [68] made an interesting observation during operation on a patient with patent ductus arteriosus and subacute bacterial endocarditis. Cultures made simultaneously of blood from the pulmonary artery and blood from the aorta showed fewer colonies of Str. viridans in the blood returning from the lungs. This provides further evidence that the lungs have an important role in filtering bacteria from the circulation.

Staphylococcic Infection.—As discussed in the section on chemotherapy, staphylococcic infections do not respond to chemotherapy as well as infections caused by other organisms; therefore attempts at specific therapy are active along other lines as well. Julianelle [69] reports further studies with the use of type A antiserum. Although in many cases in which treatment is with this agent the effects may result from nonspecific factors, there is evidence, he feels, of the participation of the type-specific anticarbohydrate factor. Serum therapy and surgical drainage are both necessary because of the inability of the serum to control localized lesions. The actual evaluation of antiserum, however, must await future trial.

The results of studies [70] on experimental bacteriophage therapy do not support the use of this substance in the treatment of staphylococcic infections. In some cases it was actually harmful.

Spink and Vivino [71] find that the coagulase test is the simplest and most reliable method for differentiating pathogenic from nonpathogenic

68. Touroff, A. S. W.: Blood Cultures from Pulmonary Artery and Aorta in Patients with Infected Patent Ductus Arteriosus, Proc. Soc. Exper. Biol. & Med. **49**:568-569 (April) 1942.

69. Julianelle, L. A.: Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia: Second Report, Ann. Int. Med. **16**:303-326 (Feb.) 1942.

70. Sulkin, S. C.; Douglass, D. D., and Bronfenbrenner, J.: Bacteriophage Therapy: IV. Effect of Bacteriophage in Experimental Staphylococcal Septicemia in Rabbits, J. Infect. Dis. **70**:92-95 (Jan.-Feb.) 1942.

71. Spink, W. W., and Vivino, J. J.: The Coagulase Test for Staphylococci and Its Correlation with the Resistance of the Organisms to the Bactericidal Action of Human Blood, J. Clin. Investigation **21**:353-356 (May) 1942.

staphylococci. Strains giving a positive reaction resist the bactericidal action of blood and are pathogenic, but even strains which give negative reactions and which are ordinarily harmless may on occasion be pathogenic and result in fatal infection. Strains giving positive reactions may yield negative reactions on subculture, and the reverse may occur, probably through the mechanism of bacterial dissociation.

Meningococci.—Branham and Carlin [72] recall how the types of meningococci in a population change from time to time. In 1936, for example, 90 per cent of strains were of group I. In 1937 group II strains increased to 16 per cent of the total number and in 1938 to 46 per cent. In later studies it appeared that yet another strain appeared which was a distinct immunologic entity but was still related to group II. The new strain comprised about 50 per cent of the strains isolated at the time.

BACILLARY DISEASES

Dysentery.—Hardy and his associates [73] report excellent results in the use of new mediums for the isolation of dysentery bacilli. They first used desoxycholate-citrate medium and later found Shiga-Salmonella agar even better. The formula of the latter is not given. The full value of either of these selective mediums is obtained when the whole surface is inoculated with the maximum amount of fecal material which will yield isolated colonies. Cultures are best obtained with material procured on rectal swabs.

This technic was applied to samples of stools from a group of 103 patients with dysentery during convalescence. Eighty-two per cent of the patients were found to be carriers. Known convalescent carrier states lasted thirty-four days on the average. In another study,[73b] of a total of over 6,000 persons in the southern states and in Puerto Rico who had had no diarrheal disorder, about 4 per cent were found to carry Shigella dysenteriae.

Macumber [74] gives a good résumé of his experience with acute bacillary dysentery in Panama. The Flexner and the Sonne type of dysentery bacillus were responsible for infection in the 263 cases studied. Specific serum therapy did not appear to be helpful.

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72. Branham, S. E., and Carlin, S. A.: Comments on a Newly Recognized Group of the Meningococcus, Proc. Soc. Exper. Biol. & Med. **49**:141-144 (Feb.) 1942.

73. (*a*) Hardy, A. V.; Watt, J., and DeCapito, T. M.: Studies of the Acute Diarrheal Diseases: VI. New Procedures in Bacterial Diagnosis, Pub. Health Rep. **57**:521-524 (April 10) 1942. (*b*) Watt, J.; Hardy, A. V., and DeCapito, T. M.: Studies of the Acute Diarrheal Diseases: VII. Carriers of Shigella Dysenteriae, ibid. **57**:524-529 (April 10) 1942. (*c*) Hardy, Watt and Peterson.[20]

74. Macumber, H. H.: Acute Bacillary Dysentery, Arch. Int. Med. **69**:624-635 (April) 1942.

An outbreak in an institution of 238 cases of acute gastroenteritis caused by Salmonella typhi murium raised several important points.[75] The source was suspected to be roast turkey, and the question was whether the birds were sick before they were killed or whether the meat was contaminated in preparation by carriers, either human or murine. Bacteria may survive and actually multiply in the center of roasted flesh or in dressing which is not heated too much to serve as a good incubator. Carrier states of infected persons may last for many weeks, contrary to previous opinion that the bacilli disappeared quickly after recovery from the disease.

Infections caused by dysentery bacilli spread slowly through a community suggesting person to person infection, while outbreaks caused by Salmonella are more explosive and without evidence of contact infection. In the outbreak just referred to the infection disappeared from the community with the termination of convalescent carrier states.

Typhoid Fever.—Botsford [76] reports a case of cholecystitis caused by the typhoid bacillus forty-three years after typhoid fever. There had been four intervening attacks of cholecystitis. Although the patient undoubtedly excreted typhoid bacilli in her stool, there is no evidence that she ever caused infection in others.

Whitfield [77] resents the implication that typhoid fever is pandemic in the southern states because of primitive sanitation. The death rate for typhoid in 1940, he points out, is about the same in Mississippi as in Connecticut, even less if only the white race is considered.

Diphtheria.—The problem of malignant diphtheria was discussed editorially.[78] Since 1927 a "new" highly fatal form of diphtheria has been encountered in Europe for which the standard prophylactic measures and antitoxin therapy were without value. Bacteriologic studies soon showed that at least three forms, or types, of diphtheria bacilli may cause the disease, namely, the mitis; the intermedius, commonly found in this country, and the gravis, which causes the severest infection. In one European epidemic the gravis type caused 96 per cent of infections. In studies by O'Meara to determine the reason for the failure of antitoxin to influence infection caused by the gravis type it was

75. Mosher, W. E.; Wheeler, S. M.; Chant, H. L., and Hardy, A. V.: Studies of the Acute Diarrheal Diseases: V. An Outbreak Due to Salmonella Typhi Murium, Pub. Health Rep. **56**:2415-2426 (Dec. 19) 1941.

76. Botsford, T. W.: Acute Typhoid Cholecystitis and Cholelithiasis Occurring Forty-Three Years After Typhoid Fever: Report of a Case, New England J. Med. **224**:799-800 (May 8) 1941.

77. Whitfield, R. N.: Typhoid in the South, Correspondence, J. A. M. A. **118**:839 (March 7) 1942.

78. Synergistic Toxins of Diphtheria Gravis, editorial, J. A. M. A. **118**:301-302 (Jan. 24) 1942. Newer Knowledge of Diphtheria Gravis, editorial, ibid. **118**:380-381 (Jan. 31) 1942.

found that the mitis form produced an antitoxin effective only against mild infections. The gravis form produces both exotoxin "A" and endotoxin "B," which together constitute the toxin necessary to evoke an antitoxin capable of controlling the infections caused by this form. The "B" factor also appears to serve as a vector for a "spreading factor" analogous to that produced by certain pathogenic cocci. One reason for the failure of commerically prepared antitoxin to influence infections caused by the gravis type seems to be that the anti-"B" component is destroyed in the process of manufacture. It is hoped that the selection of suitable strains and the proper preparation of antitoxin will serve to miminize the threat of this dangerous form of diphtheria. The first infections with Bacillus diphtheriae gravis in America appeared in Nova Scotia in 1941 but were promptly checked without evidence of further spread.

Tetanus.—A résumé on the treatment of tetanus was published. According to Spaeth,[79] the gross mortality in 96 patients was 35 per cent. No deaths occurred among patients whose temperature remained normal, but 69 per cent of those with fever died. This suggests a possible bearing of the presence of secondary infection in patients who die and of the result of the delayed effects of toxin alone in those who recover. In the author's experience sedative drugs were the keystone of treatment. An average dose of 30,000 American units of antitoxin was given but never intrathecally. He regards treatment of the local lesion as unimportant.

Gas Bacillus Infection.—The overly enthusiastic views of several authors concerning the value of roentgen therapy in the treatment of gas bacillus infection provoked timely editorial comment.[80] It is pointed out that many observers consider roentgen therapy ineffective and find no basis whatever for its use in the treatment of infections caused by gas bacilli. Well controlled clinical and experimental studies failed to show any beneficial influence of such treatment.

One author [81] reports 4 instances of infection with gas-producing bacilli in diabetic patients, yet in these cases colon bacilli, not Welch's bacilli, were the cause. The high sugar content of the blood and tissue was thought to favor the growth of these bacteria. It is probable that the matter is not quite so simply explained. Another author [82] reports

79. Spaeth, R.: Therapy of Tetanus: A Study of Two Hundred and Seventy-Six Cases, Arch. Int. Med. **68**:1133-1160 (Dec.) 1941.

80. Roentgen Therapy of Gas Bacillus Infection, editorial, J. A. M. A. **118**:230 (Jan. 17) 1942.

81. Gillies, C. L.: Interstitial Emphysema in Diabetes Mellitus Due to Colon Bacillus Infection: Report of Four Cases, J. A. M. A. **117**:2240-2242 (Dec. 17) 1941.

82. Leder, H. L.: Proteus Vulgaris as Gas Producer in Diabetes, Correspondence, J. A. M. A. **118**:664 (Feb. 21) 1942.

the bacillus Proteus vulgaris as another bacterium able to produce infection and gas in diabetic patients. These observations emphasize the importance of making etiologic diagnoses. Obviously, infections accompanied with the formation of gas are not all caused by the Welch bacillus and should not be treated as such unless they are.

Tularemia.—Francis and Felton [83] were unable to produce protective antibodies against tularemia in the serum of horses, sheep or rabbits, although specific agglutinins developed. No evidence of protective antibody was found in "convalescent" human serum. These studies do not support the use of antitularemia serum in the treatment of the disease.

Ey and Daniels [84] cite an example of a hunter and his 3 dogs who contracted tularemia from wild rabbits. The dogs acquired the infection by ingesting infected rabbit meat and became mildly sick; specific agglutinins developed in their blood.

Pasteurella tularensis may occasionally be cultivated directly from the blood of patients on blood-dextrose-cystine agar.[85]

Plague.—Although discussed previously, particularly by Rucker and by Jellison, the first proof of the transmission of plague by a bird comes from the demonstration of plague bacilli in sticktight fleas removed from burrowing owls captured in an epizootic area.[86] These fleas also infest Cooper's hawk and domestic fowl and add another complicating factor to the epidemiology of plague.

Creel,[87] like many others, still feels that plague is spreading eastward in the United States and that it could probably have been stamped out had proper measures been taken when the diagnosis was made in the "first" case. Meyer,[88] however, properly questions this concept and summarizes the known facts. There is every reason to believe that sylvatic plague has been endemic in widespread areas among wild rodents on this continent for an unknown period and can never be eradicated with the means available at present. Neither is there any reason to

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83. Francis, E., and Felton, L. D.: Antitularemic Serum, Pub. Health Rep. **57**:44-55 (Jan. 9) 1942.

84. Ey, L. F., and Daniels, R. E.: Tularemia in Dogs, J. A. M. A. **117**:2071-2072 (Dec. 13) 1941.

85. Ransmeier, J. C., and Schaub, I. G.: Direct Cultivation of Bacterium Tularense from Human Blood Drawn During Life and at Autopsy: Report of Three Fatal Cases of Tularemia with Brief Notes on Two Others, Arch. Int. Med. **68**:747-762 (Oct.) 1941.

86. Wheeler, C. M.; Douglas, J. R., and Evans, F. C.: The Role of the Burrowing Owl and the Sticktight Flea in the Spread of Plague, Science **94**:560-561 (Dec. 12) 1941.

87. Creel, R. H.: Plague Situation in the Western United States, Am. J. Pub. Health **31**:1155-1162 (Nov.) 1941.

88. Meyer, K. F.: The Known and the Unknown in Plague, Am. J. Trop. Med. **22**:9-36 (Jan.) 1942.

believe that plague will ever cause the havoc it did in past centuries, unless the complete disintegration of civilization occurs. If measures to prevent it must eventually be undertaken at some time, the most feasible method is to establish a rodent-free zone around the community in question.

Meyer also points out that there is some encouragement for the use of antiplague serum in large doses therapeutically, but that vaccine, although it may reduce mortality, has never controlled an outbreak. The relative merits of the Haffkine type of vaccine or the live "attenuated" bacilli are still unsettled. Another report [89] was made of vaccination of more than 2,000,000 subjects with living virulent plague bacilli, without harmful consequences.

Two fatal cases of plague probably contracted from ground squirrels occurred in California.[89a]

Macchiavello [90] found that plague in Brazil increased with heavy rains and decreased with drought and a dispersion of rats from a community. High atmospheric temperature also obliges the vector flea, Xenopsylla cheopis, to remain in rat nests, thus keeping plague subterranean and away from human beings until the temperature falls. Numerous other epizootic diseases occur with plague in rodents. Sylvatic plague has not yet been reported in Brazil.

In the cases of plague in human beings the disease was generally milder than "classic" plague, with less bubonic suppuration and no pneumonia. Other forms in children were characterized by mild transitory symptoms. Macchiavello described 9 cases of a "new" clinical type of plague called multiglandular fever, characterized by septicemia; fever; wasting; anemia; multiple abscesses; a prolonged course, like that previously described by Meyer, and a low mortality. A case of combined infection with Pasteurella pestis and Pasteurella pseudotuberculosis rodentium was included in the series reported by Macchiavello.

Another case, the sixth, of infection with Past. pseudotuberculosis rodentium was reported [91] in the United States.

Leprosy.—After many previous unsuccessful or supposedly successful but unrecognized trials, attempts to transmit leprosy to experimental

89. Otten, L.: A Live Plague Vaccine and the Results, Mededeel. v. d. dienst. d. volksgezondh. in Nederl.-Indië **30**:61, 1941.

89a. Plague Infection Reported in the United States During 1941, Pub. Health Rep. **57**:903-905 (June 12) 1942.

90. Macchiavello, A.: Some Special Epidemiological and Clinical Features of Plague in Northeastern Brazil, Pub. Health Rep. **56**:1657-1661 (Aug. 15) 1941.

91. Moss, E. S., and Battle, J. D.: Human Infection with Pasteurella Pseudotuberculosis Rodentium of Pfeiffer: Report of Case, Am. J. Clin. Path. **11**:677-699 (Sept.) 1941.

animals were revived by two investigators. Loving [92] caused chronic lesions in rabbits after inoculation with Duval's chromogenic acid-fast strain of Bacillus leprae. Nodules developed at the site of inoculation, and bacilli were present in the necrotic areas for as long as eight to nine months. Fite [93] inoculated 154 rats with emulsions of lepromatous nodules from human beings together with mucin or agar. Of these rats, a leprous process developed in 6 at the site of infection after eighteen months.

A fatal case of infection with Bacillus violaceus was reported.[94]

VIRUS DISEASES

Colds and Influenza.—Few persons realize the amount of time lost through mild infections of the respiratory tract. One study of the subject, conducted by the American Institute of Public Opinion,[95] shows an estimated total of 18,000,000 cases in one week in December.

Spiesman [96] gave massive doses of vitamin A and vitamin D separately to two groups of persons, but no effect either on the prevention or on the severity of colds was noted. When the two vitamins were combined, however, colds were significantly reduced, though it is hard to see why, and one wonders what method of control was used.

Influenza.—A new strain of influenza virus, different from virus A but closely related to virus B, was isolated during an epidemic in California.[97] Several other epidemic outbreaks were reported. Influenza A predominated in Boston in the winter of 1940-1941,[98] but in many cases there was no evidence of infection either with A or with B virus, suggesting that still other unidentified agents may be operative.

92. Loving, W. L.: The Experimental Infection of Rabbits with Duval's Chromogenic Acid-Fast Bacillus from Human Leprosy, J. Infect. Dis. **68**:193-206 (May-June) 1941.

93. Fite, G. L.: Development of a Leprous Process in Rats at the Site of Inoculation with Material from Human Leprosy, Pub. Health Rep. **56**:1919-1922 (Sept. 26) 1941.

94. Schattenberg, H. J., and Harris, W. H.: A Definite and Unique Occurrence of Rapidly Fatal Infections Caused by Bacillus Violaceus Manilae, J. A. M. A. **117**:2069-2070 (Dec. 13) 1941.

95. Gallup Survey of Common Colds, Medical News, J. A. M. A. **118**:241 (Jan. 17) 1942.

96. Spiesman, I. G.: Massive Doses of Vitamins A and D in Prevention of Common Cold, Arch. Otolaryng. **34**:787-791 (Oct.) 1941.

97. Eaton, M. D., and Beck, M. D.: A New Strain of Influenza B Isolated During an Epidemic in California, Proc. Soc. Exper. Biol. & Med. **48**:177-180 (Oct.) 1941.

98. Pearson, H. E.; Eppinger, E. C.; Dingle, J. H., and Enders, J. F.: A Study of Influenza in Boston During the Winters 1940-41, New England J. Med. **225**: 763-770 (Nov. 13) 1941.

Influenza preceded and apparently predisposed many patients to pneumococcic and staphylococcic pneumonia. Similar findings were reported by Lennette and his associates [99] in fifteen observed epidemics. Influenza A was causally related to more than 50 per cent of cases; influenza B, to only a few, and in 30 per cent of cases no virus was isolated. Epidemics apparently have diverse causes, and several types of virus are usually operative. The demonstration of one virus alone does not prove that the disease is of the same origin in all cases. Andrewes and associates [100] report influenza A virus as causing 79 per cent of infections in one epidemic in England. In a later study [101] evidence of the participation of influenza B was present. In more than half the cases in one epidemic the disease was caused by some agent other than influenza virus A or B.

An epidemic influenza-like disease in Minnesota in May 1939 could not be identified with influenza A.[102] Subsequent tests on nasopharyngeal washings kept frozen for nineteen months revealed the presence of influenza B. Serologic tests showed that the number of subclinical infections was equal to the number of persons actually sick. The clinical features of influenza A are so similar to those of influenza B as to be indistinguishable.

Influenza Vaccine.—Intensive studies were made to test the value of the vaccines already developed and to bring about an improvement in the technic in the hope of providing a more efficient method of prophylaxis. With methods in use at present the reported reduction of 50 per cent in the incidence of influenza A, as recorded by Horsfall's group,[103] is not great enough to control the disease. The specific antibodies evoked by vaccine were often of a titer equal to that encountered in normal persons, and protection against influenza was in direct proportion to the increase of demonstrable antibodies. Unfortunately, infection with the virus of influenza A was not prevented in all cases by vaccination with complex influenza A vaccine, and as would be expected, the incidence of influenza caused by virus B and influenza of unknown cause was not affected in the group studied.

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99. Lennette, E. H.; Rickard, E. R.; Hirst, G. K., and Horsfall, F. L.: Diverse Etiology of Epidemic Influenza, Pub. Health Rep. **56**:1777-1787 (Sept. 5) 1941.

100. Andrewes, C. H.; Glover, R. E.; Hudson, W. P.; Lush, D., and Stuart-Harris, C. H.: Influenza in England in 1940-41, Lancet **2**:387-388 (Oct. 4) 1941.

101. Lush, D.; Stuart-Harris, C. H., and Andrewes, C. H.: The Occurrence of Influenza B in Southern England, Brit. J. Exper. Path. **22**:302-304 (Dec.) 1941.

102. Nigg, C.; Eklund, C. M.; Wilson, D. E., and Crowley, J. H.: Study of an Epidemic of Influenza B, Am. J. Hyg. **35**:265-284 (March) 1942.

103. Horsfall, F. L.; Lennette, E. H.; Rickard, E. R., and Hirst, G. K.: Studies on the Efficacy of a Complex Vaccine Against Influenza A, Pub. Health Rep. **56**: 1863-1875 (Sept. 19) 1941.

Experiments made in California [104] to test the relative value of Horsfall's complex distemper-influenza A virus vaccine and a living virus vaccine failed to show significant differences. In one test one vaccine gave slightly better results, and in the second, the other. The results of another group [105] of investigators were similar and led the authors to state that none of the many experiments with active and with inactive virus has resulted in conclusive proof of the effectiveness of vaccine against influenza A. Nevertheless, in these studies there was a reduction of incidence of the disease in a vaccinated group (13 to 15 per cent) as compared with controls (25 to 43 per cent), but influenza A developed subsequently in several vaccinated persons.

The results of a further study [106] at Letchworth Village, N. Y., are discouraging. Specific resistance in the interepidemic period could not be increased with vaccine. Influenza A occurred later not only among those persons recently vaccinated but in those vaccinated for four successive years. There was no significant difference in the incidence of acute disease of the respiratory tract among the inoculated persons and that in the controls. Nor was there a significant rise in the complement-fixing titer for influenza A after inoculation and subsequent infection. The incidence of influenza A was the same in persons with high or low titer. Clinical infection during one season also failed to protect against succeeding attacks.

Other studies [107] were made to test the nonspecific effect of the usual gamut of bacteria contained in commercially prepared so-called "cold" vaccines added to specific influenza vaccine, but no evidence of an adjuvant effect was noted.

According to Eaton and Martin,[108] the allantoic fluid vaccine for influenza B inactivated by formaldehyde was effective in evoking a rela-

104. Martin, W. P., and Eaton, M. D.: Experiments on Immunization of Human Beings Against Influenza A, Proc. Soc. Exper. Biol. & Med. **47**:405-409 (June) 1941.

105. Brown, J. W.; Eaton, M. D.; Meiklejohn, G.; Lagen, J. B., and Kerr, W. J.: An Epidemic of Influenza: Results of Prophylactic Inoculation of a Complex Influenza A-Distemper Vaccine, J. Clin. Investigation **20**:663-669 (Nov.) 1941.

106. Siegel, M.; Muckenfuss, R. S.; Schaeffer, M.; Wilcox, H. L., and Leider, A. G.: A Study in Active Immunization Against Epidemic Influenza and Pneumococcus Pneumonia at Letchworth Village: IV. Results in an Epidemic of Influenza A in 1940-1941, Am. J. Hyg. **35**:186-230 (March) 1942.

107. Ungar, J., and Hunwicke, R. F.: The Value of the Non-Specific Factor in Experimental Immunization with Influenza Virus, Brit. M. J. **2**:12-13 (July 5) 1941.

108. Eaton, M. D., and Martin, W. P.: Immunization with Inactive Virus of Influenza B: Comparison of Antibody Response with That Produced by Infection, Pub. Health Rep. **57**:445-451 (March 27) 1942.

tively high antibody response in human subjects, but since the complement-fixing antibodies were weaker, the antigenic stimulus of vaccine was different from that of actual infection. The effectiveness of any vaccine is not necessarily dependent on the measurable antibody response.

Attempts were made to control influenza by the use of aerosols sprayed into the air.[109] Robertson and his associates [110] found the vapor of propylene glycol effective in preventing influenza in mice placed in an atmosphere laden with influenza virus in fine suspension.

Studies on the mode of spread of infection with influenza virus confirmed the important views of Wells that infection may be conveyed by means other than visible droplets expelled from the respiratory tract. Andrewes and Glover [111] placed normal ferrets and ferrets inoculated with influenza A virus in closed spaces, yet separated so as to prevent direct spraying with infected droplets. In spite of this barrier the exposed animals contracted the disease, presumably from microscopic particles of virus wafted through the air. When adequate ventilation was provided, with windows left open, no cross infection took place.

Glover [112] made similar experiments but with double infection by influenza virus and hemolytic streptococci, which were thought to play so important a role in the epidemic of 1918-1919. Normal ferrets easily contracted the dual infection when placed in cages with infected animals, but if they were separated from them by a barrier, only the influenza infection was transmitted, unless the recipient animals had previously been inoculated with influenza virus. Under the last-named circumstances the injurious action of influenza on the mucous membrane seemed to be specific in preparing the field for the invasion of streptococci, since irritation with chemicals failed to do so.

The amount of influenza virus suspended in air seemed to be important in direct proportion to the degree of severity of resultant infection in exposed animals.[113] A heavy suspension caused the death of all

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109. Henle, W., and Zellat, J.: Effect of Propylene Glycol Aerosol on Air-Borne Virus of Influenza A, Proc. Soc. Exper. Biol. & Med. **48**:544-547 (Nov.) 1941.

110. Robertson, O. H.; Loosli, C. G.; Puck, T. T.; Bigg, E., and Miller, B. F.: The Protection of Mice Against Infection with Air-Borne Influenza Virus by Means of Propylene Glycol Vapor, Science **94**:612-613 (Dec. 26) 1941.

111. Andrewes, C. H., and Glover, R. E.: Spread of Infection from the Respiratory Tract of the Ferret: I. Transmission of Influenza A Virus, Brit. J. Exper. Path. **22**:91-97 (April) 1941.

112. Glover, R. E.: Spread of Infection from the Respiratory Tract of the Ferret: II. Association of Influenza A Virus and Streptococcus Group C, Brit. J. Exper. Path. **22**:98-107 (April) 1941.

113. Wells, W. F., and Henle, W.: Experimental Air-Borne Disease: Quantitative Inoculation by Inhalation of Influenza Virus, Proc. Soc. Exper. Biol. & Med. **48**:298-301 (Oct.) 1941.

mice; a less heavy one caused pulmonary lesions only, and a dilute suspension failed to cause infection at all. When type I pneumococci were added to the spray simultaneously or five days later, the resulting pulmonary infections were more severe. The pulmonary lesions, however, looked the same as in those animals infected with virus alone.

The level of specific neutralizing antibodies in the blood of normal persons is said to be of value in determining their susceptibility to influenza A or B.[114] The relation is specific, since a high level of antibodies to one virus does not indicate resistance to the other or to influenza-like disease of undetermined origin. In one study [115] a sharp increase in virus-inactivating bodies developed in the nasal secretion in 9 of 10 patients with influenza A. The response was often parallel to the increase of similar antibodies in the blood and indicates that an important immune mechanism exists in nasal secretions.

Influenza virus was present in the feces of mice three days after intranasal inoculation.[116] It is probable, of course, that the virus was merely coughed up and swallowed, but the possibility of actual multiplication in the gastrointestinal tract was raised.

Interesting experiments [117] were made to determine the effects of various conditions which supposedly reduce resistance to infection with influenza. An unusual degree of heat, of cold and of fatigue failed to make test mice more susceptible to infection than control animals. This experience is in line with observations made on human beings in the epidemic of 1918-1919, when influenza occurred regardless of the physical condition of the victims. Severe deficiency either of vitamin A or of vitamin C likewise failed to have any effect on the level of demonstrable antibodies for influenza or on the phagocytic activity of leukocytes in human subjects.[118]

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114. Rickard, E. R.; Horsfall, P. L.; Hirst, G. K., and Lennette, E. H.: The Correlation Between Neutralizing Antibodies in Serum Against Influenza Viruses and Susceptibility to Influenza in Man, Pub. Health Rep. **56**:1819-1834 (Sept. 12) 1941.

115. Francis, T., and Brightman, I. J.: Virus-Inactivating Capacity of Nasal Secretions in the Acute and Convalescent Stages of Influenza, Proc. Soc. Exper. Biol. & Med. **48**:116-117 (Oct.) 1941.

116. Sarracino, J. B., and Soule, M. B.: Isolation of Virus from Fleas of Mice Receiving Intranasal Inoculations of Epidemic Influenza Virus, Proc. Soc. Exper. Biol. & Med. **48**:188-191 (Oct.) 1941.

117. Sarracino, J. B., and Soule, M. H.: Effect of Heat, Cold, Fatigue and Alcohol on Resistance of Mice to Human Influenza Virus, Proc. Soc. Exper. Biol. & Med. **48**:183-186 (Oct.) 1941.

118. Feller, A. E.; Roberts, L. B.; Ralli, E. P., and Francis, T.: Studies on the Influence of Vitamin A and Vitamin C on Certain Immunological Reactions in Man, J. Clin. Investigation **21**:121-137 (March) 1942.

"Virus" Pneumonia.—Two minor outbreaks, both in schools, were reported [119] of the disease, called for convenience "virus" pneumonia. Adams and his associates [120] studied a second epidemic of a severe form of "primary virus pneumonitis" among young infants, with a mortality rate of 14 per cent. Cytoplasmic inclusion bodies were present in the epithelial cells in the lungs of the infants who died and in cells in smears of material from the throats of 85 per cent of the others. No virus was isolated.

In several attempts to discover the cause of this disease, or group of diseases, numerous agents have been isolated, as mentioned in last year's review.[121] More recent studies have provided further interesting data. The virus isolated last year by Eaton and his co-workers from patients with atypical pneumonia was found to be antigenically related to the viruses of both psittacosis and meningopneumonitis.[122] Similarities and relations to the virus of lymphogranuloma venereum were also detected.[123] All four viruses cause pneumonia and meningitis in inoculated animals, are characterized by the formation of elementary bodies and have antigenic components common to each other. Of interest also is the report of positive complement fixation reactions in the blood of patients convalescent from atypical pneumonia with antigen from the virus of lymphogranuloma venereum and of meningopneumonitis, and in 5 of 8 cases of "virus pneumonia" the result of the Frei test was positive. The numerous apparent similarities of these viruses and of the diseases they cause both in human beings and in animals seem too convincing to regard the relation as coincidental. It has even been suggested that the viruses of psittacosis, a psittacosis-like disease, meningopneumonitis and lymphogranuloma venereum may have arisen from an original strain in the animal kingdom and have become diversified or modified by the invasion of or adaptation to various hosts.[122] What relation these viruses may have to some or to most cases of the so-called "virus" pneumonia is a matter of further test. It is possible that mem-

119. Gallagher, J. R.: Acute Pneumonitis: Report of an Epidemic, Yale J. Biol. & Med. **13**:769-781 (July) 1941. Daniels, W. B.: Bronchopneumonia of Unknown Etiology in a Girls' School, Am. J. M. Sc. **203**:263-276 (Feb.) 1942.

120. Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: A Comparative Study of Two Epidemics, J. Pediat. **20**:405-420 (April) 1942.

121. Reimann, H. A.: Infectious Diseases: A Review of Significant Publications in 1940-1941, Arch. Int. Med. **68**:325-368 (Aug.) 1941.

122. Eaton, M. D.; Martin, W. P., and Beck, M. D.: The Antigenic Relationship of the Viruses of Meningopneumonitis and Lymphogranuloma Venereum, J. Exper. Med. **75**:21-33 (Jan.) 1942.

123. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **48**:528-531 (Nov.) 1941.

bers of the psittacosis group of viruses do cause certain instances of the syndrome called "virus" pneumonia.

Meyer and associates [124] reported the isolation of a psittacosis-like virus from the lung of a patient who had been exposed to pigeons. A similar virus was recovered from some of the pigeons, and the complement fixation reaction for psittacosis was positive in 63 per cent of the birds. In another study [125] a case of pneumonia in a patient living on a chicken farm where an epidemic disease among poultry existed led to an epidemiologic survey. Many of the chickens were found to be spontaneously infected with the psittacosis-like virus, and serum from other members of the family, who were not sick, gave a positive complement fixation reaction for psittacosis. Meyer names this psittacosis-like virus disease "ornithosis," to distinguish it from true psittacosis. Evidence of its widespread distribution among birds and poultry he feels renders it likely that human beings are occasionally infected and disease develops which is erroneously called "virus" pneumonia. Although psittacosis virus and the related ones discussed in a previous paragraph pass through certain filters, they have other characteristics, such as microscopicaliy visible particles, which place them in a class apart from true filtrable viruses, and the pneumonia they cause should not be named "virus" pneumonia.

For the isolation of ornithosis virus from human sputum intracranial injection into mice or pigeons may be essential, although it is probable that intranasal injection into mice would be successful.[125a] Intraperitoneal injection may give negative results.

Alicandri [126] reports a case of psittacosis in a man whose only known contact with possible sources was with pigeons. The data given do not tell the nature of the contact. The patient's serum gave a positive complement fixation reaction to psittacosis in a dilution of 1 : 256.

In my own experience this year with 8 cases of "virus" pneumonia, the complement fixation reaction for psittacosis was moderately positive in 3 and strongly positive in 1, although nothing in the case histories indicated contact or association with the known carriers of the psittacosis or the ornithosis virus. Inoculation of sputum into mice gave no evi-

124. Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, Proc. Soc. Exper. Biol. & Med. **49**:609-615 (April) 1942.

125. Meyer, K. F., and Eddie, B.: Spontaneous Ornithosis (Psittacosis) in Chickens the Cause of a Human Infection, Proc. Soc. Exper. Biol. & Med. **49**:522-525 (April) 1942.

125a. Pinkerton, H., and Moragues, V.: Comparative Study of Meningopneumonitis Virus, Psittacosis of Pigeon Origin and Psittacosis of Parrot Origin, J. Exper. Med. **75**:575-580 (June) 1941.

126. Alicandri, H.: Psittacosis, J. A. M. A. **118**:1214 (April 4) 1942.

dence of presence of psittacosis as it is usually described. The Frei test performed in a few cases gave negative results. The positive complement fixation reactions suggest that one of the viruses of the psittacine group may have caused the disease.

Smadel and his associates [127] report 2 unusual fatal cases of lymphocytic choriomeningitis, in which the diagnosis was obscure clinically and was made only after the isolation of the virus from the brain, the blood and the lungs at necropsy. In both cases the outstanding postmortem observation was a patchy bronchopneumonia characterized chiefly by a mononuclear cell infiltrate. Thus is added another entity to the syndrome called "virus" pneumonia. The blood of 1 of my patients with "virus" pneumonia was strongly protective against the virus of lymphocytic choriomeningitis.

It appears now that the term "virus" pneumonia is justified to name a syndrome composed of numerous etiologic entities. The pneumonias caused by viruses of influenza, chickenpox, lymphocytic choriomeningitis and perhaps the mongoose-infecting virus can be included in this group. The psittacine group of viruses may cause a similar clinical form of pneumonia but are not regarded as true filtrable viruses by some, and other agents not viruses, such as the Rickettsia of "Q" fever, the protozoan Toxoplasma and the fungus Coccidioides immitis, may give rise to atypical pneumonia which is in many respects similar to those caused by viruses.

It appears from my own studies and from those of other investigators that still other unidentified forms of atypical pneumonia exist, which can be classified only after the etiologic agents are discovered. In an official statement [128] the Surgeon General of the Army proposes the term primary atypical pneumonia, etiology unknown, to classify the syndrome of "virus" pneumonia encountered in the Army medical service. The recommendation is good, but this designation need not be used in cases in which the etiologic agent is determined.

Chickenpox.—Two cases of severe chickenpox in adults, 1 fatal, were reported.[129] Pneumonia occurred in both cases, and at necropsy in 1 there was encountered a mononuclear cell exudate with the formation of alveolar linings, both of which were at one time thought to be characteristic of virus infection of the lung, but other irritants are now known

127. Smadel, J. E.; Green, R. H.; Paltauf, R. M., and Gonzales, T. A.: Lymphocytic Choriomeningitis: Two Human Fatalities Following an Unusual Febrile Illness, Proc. Soc. Exper. Biol. & Med. **49**:683-686 (April) 1942.

128. Primary Atypical Pneumonia, Etiology Unknown, Official Statement, War Med. **2**:330-333 (March) 1942.

129. Waring, J. J.; Neubuerger, K., and Geever, E. F.: Severe Forms of Chickenpox in Adults, with Autopsy Observations in a Case with Associated Pneumonia and Encephalitis, Arch. Int. Med. **69**:384-408 (March) 1942.

to cause similar changes. Acute toxic encephalitis and nephrosis were also present.

Poliomyelitis.—A number of important contributions to the knowledge of poliomyelitis were made, some of them contradictory, but all will probably fit finally into the complex pattern.

Report of detailed studies by Howe and Bodian fills most of the August 1941 number of *The Bulletin of the Johns Hopkins Hospital.* In essence, their work indicates that there may be various portals of entry of the virus. In most of a series of fatal cases the olfactory bulbs were not invaded, suggesting that the virus entered elsewhere than the respiratory tract. The alimentary tract appears to be an important focus for the proliferation of the virus, and the spinal cord, the primary site of invasion of the central nervous system. In experimental studies cutting the spinal cord and sympathetic nerves did not hinder the spread of the virus to other parts of the nervous system, indicating a possible transit through the lymphatics, the blood or unusual pathways, such as the vagus nerve. The virus was estimated to travel along nerves at the rate of 2.4 mm. per hour. In other experiments clinical evidence of the disease appeared to be arrested at any stage after invasion of the nervous system. Since the spinal cord is not always involved, symptoms of encephalitis alone may occur without paralysis and give rise to diagnostic confusion, particularly with other specific forms of encephalitis (see p. 163).

Sabin and Ward [130] investigated the excretion of the virus in the early stages of poliomyelitis and tried to find its source. The virus was regularly present in the stools but was not found in the nasal or the oral secretion or in the urine. The virus, therefore, probably does not get into the stool simply because it has been swallowed. It is much more likely to have originated from the walls of the digestive tract. The virus apparently does not invade the nervous system by way of the nose or multiply in the nervous system, since it was present in pharyngeal and in intestinal tissue but not in the nasal mucosa or in the olfactory bulbs.

Other observers [131] recovered the virus at necropsy from the contents of the colon in 26 per cent of patients, from the stools in 20 per cent of living patients and from the stools in 5 per cent of healthy persons in contact with patients. Virus was present in the tonsil-adenoid tissue, the spinal cord and the colonic contents in 73 per cent of patients who

130. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: II. Elimination of Virus, J. Exper. Med. **74**:519-530 (Dec.) 1941.

131. Kessel, J. F.; Moore, F. J.; Stimpert, F. D., and Fisk, R. T.: Occurrence of Poliomyelitis Virus in Autopsies, Patients and Contacts, J. Exper. Med. **74**:601-610 (Dec.) 1941.

died. Repeated examinations of the stools of 5 patients failed to reveal the presence of the virus after a month.

McClure and Langmuir [132] made studies to determine how frequently the virus of poliomyelitis appears in the feces of persons in a community when cases of the disease occur. Specimens from 40 persons were tested, including ones from 5 persons with clinical evidence of poliomyelitis. Stools from 20 of 27 contacts contained the virus.

Interesting experiments were made in studying the nature of airborne poliomyelitis in monkeys.[133] Typical poliomyelitis developed in 10 of 60 monkeys exposed to virus suspended in air. Of these, 4 had had olfactory "blockade" with zinc sulfate solution and 6 had not. Examination of the olfactory bulbs in those not treated showed histologic lesions in each, but they were at times so slight as to suggest secondary rather than primary lesions and may not indicate the entrance of virus at this point. Because the olfactory route was excluded in 2 significant instances, and because the oropharyngeal and gastrointestinal routes have been excluded by long experience, it is highly probable that the portal of entry in rhesus monkeys, at least, is in the mucosa of the lower respiratory tract at or below the epiglottis, and in cynomolgus monkeys, in the oropharynx. The experiments suggest that poliomyelitis in human beings may in some cases be air borne and the lungs the portal of entry. The known presence of virus in the nasopharynx providing a source for air contamination and previous evidence of apparent contact infection support the suggestion. Infection may occur both through the respiratory tract and through the gastrointestinal tract. A case of poliomyelitis developing in a laboratory worker was reported.[134]

Further evidence of the importance of infection through human contact is supplied by Piszczek and his associates [135] in Chicago and by Casey,[136] who studied an epidemic in a sparsely populated area of Alabama. The spread of the disease from neighborhood to neighborhood and from person to person seemed in Casey's study to be directly related to human travel. The effective reservoir of the virus appeared, as in other contagious diseases, to be a patient within three days before

132. McClure, G. Y., and Langmuir, A. D.: Search for Carriers in an Outbreak of Acute Anterior Poliomyelitis in a Rural Community: The Incidence of Virus in Feces, Am. J. Hyg. **35**:385-391 (March) 1942.

133. Faber, H. K., and Silverberg, R. J.: Experimental Air-Borne Infection with Poliomyelitis Virus, Science **94**:566-568 (Dec. 12) 1941.

134. Sabin, A. B., and Ward, R.: Poliomyelitis in a Laboratory Worker Exposed to the Virus, Science **94**:113-114 (Aug. 1) 1941.

135. Piszczek, E. A.; Shaughnessy, H. J.; Zichis, J., and Levinson, S.: Anterior Poliomyelitis: Study of an Outbreak in West Suburban Cook County, Ill.; Preliminary Report, J. A. M. A. **117**:1962-1965 (Dec. 6) 1941.

136. Casey, A. E.: Observations in an Epidemic of Poliomyelitis, Science **95**: 359-360 (April 3) 1942.

or three days after the onset of the first prodromal symptom. The actual mode of infection was not discovered.

Lumsden's study[137] in Mississippi led to opposite conclusions. Epidemiologic studies suggested that the disease was spread not by personal contact but by unknown factors. These factors may include rats, mice, domestic fowl, cattle and flies or other insects.

In the course of the study the author encountered many erroneous diagnoses. Colds, coryza, tonsillitis, rheumatic fever, diarrhea, malaria and other disorders were called poliomyelitis. A few physicians even depended on a cutaneous reaction to Rosenow serum for the diagnosis. The number of wrong diagnoses exceeded the number of unreported cases later added to the series.

Studies are also being continued on the possibility of fly-borne infection. In one of them poliomyelitis virus was isolated in 2 instances from flies trapped in an environment where the disease occurred.[138] Toomey and his associates,[139] after many failures, also report isolation of the virus from flies trapped near a sewer. They apparently do not consider flies as an important factor, because the virus could not be consistently recovered from them in epidemic years, the disease does not always occur in crowded communities infested with flies and the peaks of epidemics do not always coincide with periods of greatest fly population.

Sabin and Ward[140] defend their views against opposing comments of Professor C. T. Brues, who minimizes the role of human contact in the causation of poliomyelitis. These authors regard poliomyelitis as resembling typhoid fever, for example, in which the chief reservoir is in human excreta and both direct and insect spread may be possible. They again point out that the disease also occurs in winter when flies are not responsible. To these views may be added the possibility of droplet infection, as discussed previously.

As in Lumsden's experience last year,[141] a South American[142] observed cases of poliomyelitis in human beings intimately associated with an acute infectious paralytic disease in poultry. A possible relation between the two diseases is obviously suggested.

137. Lumsden, L. L.: An Epidemiological Study of Poliomyelitis in Mississippi in 1941, Pub. Health Rep. **57**:729-753 (May 15) 1942.

138. Paul, J. R.; Trask, J. D.; Bishop, M. B., and Melnick, J. L.: The Detection of Poliomyelitis Virus in Flies, Science **94**:395-396 (Oct. 24) 1941.

139. Toomey, J. A.; Takacs, W. S., and Tischer, L. A.: Poliomyelitis Virus from Flies, Proc. Soc. Exper. Biol. & Med. **48**:637-639 (Dec.) 1941.

140. Sabin, A. B., and Ward, R.: Insects and Epidemiology of Poliomyelitis, Science **95**:300-301 (March 20) 1942.

141. Lumsden, L. L.: "Sporadic" Poliomyelitis, Pub. Health Rep. **56**:992-1007 (May 9) 1941.

142. Preioni, C.: Origin of Acute Anterior Poliomyelitis, Rev. Asoc. méd. argent. **55**:676 (Sept. 15-30) 1941.

The relation of tonsillectomy and poliomyelitis was the subject of a recent review [143] and of editorial comment.[144] The striking difference in the number of instances of the bulbar form, 27 per cent, in tonsillectomized children, as compared with 4.2 per cent in children with tonsils, is referred to. Nonparalytic poliomyelitis apparently occurs in either group just as often as the bulbar and the spinal form combined. The removal of tonsils seems, therefore, to be determinant between the bulbar and the spinal type of the disease. The nasopharyngeal mucosa seems to be particularly vulnerable to invasion, and tonsillectomy should not be performed when poliomyelitis is prevalent.

Rosenow [145] used the new electron microscope to bolster his theory concerning the relation of streptococci and their filtrable forms to the cause of poliomyelitis. The granules shown in his photomicrographs, however, and in the preparations viewed by others are not distinctive of material from patients with poliomyelitis and cannot be interpreted as being specifically related to the disease.

Treatment: In another editorial [146] the subject of massage is discussed in treatment of the disease. Massage is clearly indicated if all motor units in paralyzed muscles are to retain their maximal physiologic activity, since muscle fibers are dependent for normal stimulation on their local reflexes and immobilization arrests the flow of these proprioceptive impulses as effectively as it abolishes the flow of lymph.

Two papers [147] advocate the adoption of the Kenny treatment of poliomyelitis as the fundamental treatment of the disease which should be instituted as soon as the diagnosis is established.

In an attempt to reevaluate the action of human convalescent serum in the prevention of poliomyelitis Kramer [148] was able to cause significant protection even if mice were treated twenty-four hours after cerebral inoculation. This is the first definite experimental evidence of the protective value of serum. There was no evident therapeutic effect. In

143. Aycock, W. L.: Tonsillectomy and Poliomyelitis, Medicine **21**:65-94 (Feb.) 1942.

144. Tonsillectomy and Poliomyelitis, editorial, J. A. M. A. **118**:980-981 (March 21) 1942.

145. Rosenow, E. C.: Microdiplococci in Filtrates of Natural and Experimental Poliomyelitic Virus Compared Under the Electron and Light Microscopes, Proc. Staff Meet., Mayo Clin. **17**:99-106 (Feb. 18) 1942.

146. Physiologic Anatomy of Poliomyelitis, editorial, J. A. M. A. **117**:1980-1981 (Dec. 6) 1941.

147. Pohl, J. F.: Kenny Treatment of Poliomyelitis, J. A. M. A. **118**:1428-1433 (April 25) 1942. Daly, M. M. I.; Greenbaum, J.; Reilly, E. T.; Weiss, A. M., and Stimson, P. M.: The Early Treatment of Poliomyelitis with an Evaluation of the Sister Kenny Treatment, ibid. **118**:1433-1443 (April 25) 1942.

148. Kramer, S. D.: Protection in White Mice with Human Convalescent Serum Against Infection with Poliomyelitis Virus (Armstrong Strain), Proc. Soc. Exper. Biol. & Med. **48**:287-293 (Oct.) 1941.

another study [149] there was no evidence as to the effect of vitamin D on the spread of poliomyelitis along peripheral nerves.

Encephalitis.—The subject was recently reviewed by Dingle.[150] According to Leake,[151] the greatest epidemic of encephalitis on record occurred in the summer of 1941 in the north central states and adjacent Canadian provinces. In North Dakota there were 1,080 cases, an incidence of 167 per hundred thousand persons, and in Nebraska the fatality rate was 16 per cent. In general, the symptomatology was like that of the St. Louis type of encephalitis. The virus of western equine encephalitis was the principal cause, as proved by the serum neutralization test. Since the great majority of infections occurred in men, particularly those working in wheat fields, some insect vector and a source other than human beings and horses are suggested. The virus was indeed isolated from a prairie chicken shot during the epidemic.[152] In Arizona [153] a smaller epidemic was apparently caused by the virus both of equine and of St. Louis encephalitis, in this case predominantly the virus of the latter. A similar dual epidemic was studied in the Yakima Valley, Wash., by Hammon and Howitt.[154]

Hammon, Carle and Izumi [155] present further evidence that the virus called the St. Louis type is as much "equine" as those called eastern and western equine strains but manifests neurotropic tendencies much less often. In inoculation experiments with the St. Louis strain the authors failed to cause clinical symptoms in horses but did produce inapparent, or subclinical, infection resulting in the presence of virus in the blood and a high titer of serum antibody.

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149. Sabin, A. B.; Ward, R.; Rapaport, S., and Guest, G. M.: Neuroinvasiveness of Poliomyelitis Virus in Relation to Vitamin D Nutrition, Proc. Soc. Exper. Biol. & Med. **48**:451-454 (Nov.) 1941.

150. Dingle, J. H.: The Encephalitides of Virus Etiology, New England J. Med. **225**:1014-1022 (Dec. 25) 1941.

151. Leake, J. P.: Epidemic of Infectious Encephalitis, Pub. Health Rep. **56**: 1902-1905 (Sept. 26) 1941.

152. Cox, H. R.; Jellison, W. L., and Hughes, L. F.: Isolation of Western Equine Encephalitis Virus from Naturally Infected Prairie Chicken, Pub. Health Rep. **56**:1905-1906 (Sept. 26) 1941.

153. Meiklejohn, G., and Hammon, W. M.: Epidemic of Encephalitis, Predominantly of the St. Louis Type in Pinal County, Ariz., J. A. M. A. **118**:961-964 (March 21) 1942.

154. Hammon, W. M., and Howitt B. F.: Epidemiological Aspects of Encephalitis in the Yakima Valley, Washington: Mixed St. Louis and Western Equine Types, Am. J. Hyg. **35**:163-185 (March) 1942.

155. Hammon, W. M.; Carle, B. N., and Izumi, E. M.: Infection of Horses with St. Louis Encephalitis Virus, Experimental and Natural, Proc. Soc. Exper. Biol. & Med. **49**:335-340 (March) 1942.

In other studies [156] made in the Pacific Northwest, specific antibodies against both St. Louis encephalitis and western equine encephalitis were found in the blood of about 50 per cent of domestic fowl and in 20 per cent of quails, robins, sparrows, doves, hawks and other wild birds. Antibodies were also found in 51 per cent of horses, cows, sheep, pigs and other domestic animals except the cat. Tests were positive in only 8 per cent of rodents. Similar observations were made by Howitt and van Herick.[157] These investigators find it difficult to understand why fowl which possess antibodies are susceptible to infection with either virus. The demonstrable immune bodies, it appears, may not always signify previous infection. There is also no need to suppose that the St. Louis variety suddenly spread to the Pacific Coast. It is more likely that the disease is widely endemic and should not have received a limiting geographic name.

Parallel searches for evidence of infection in insects were made. Hammon and his co-workers [158] found the virus both of St. Louis and of Western equine encephalitis in the mosquito Culex tarsalis in the epidemic area. Ticks may be experimentally infected,[159] and Wheeler [160] in Kansas reports studies in which the virus of western equine encephalitis was found in 50 per cent of assassin bugs (Microtonus purcis), which feed on human beings and animals, possibly horses and rodents. He reports the case of a boy whose illness had after-effects typical of ones often occurring in cases of anterior poliomyelitis; the blood gave a strongly positive reaction for Western equine encephalitis. This occurrence indicates a type of mistake in diagnosis which is probably not uncommon.

In discussing the control of the three known American encephalitides, the St. Louis, the eastern equine and the western equine form, Hammon [161] suggests that the three be considered as closely related, since

156. Hammon, W. M.; Gray, J. A.; Evans, F. C.; Izumi, E. M., and Lundy, H. W.: Western Equine and St. Louis Encephalitis Antibodies in the Sera of Mammals and Birds from an Endemic Area, Science **94**:305-307 (Sept. 26) 1941.

157. Howitt, B. F., and van Herick, W.: Neutralizing Antibodies Against St. Louis and Western Equine Encephalitic Viruses in Horses and Fowl, Proc. Soc. Exper. Biol. & Med. **48**:247-250 (Oct.) 1941.

158. Hammon, W. M.; Reeves, W. C.; Brookman, B.; Izumi, E. M., and Gjullin, C. M.: Isolation of the Viruses of Western Equine and St. Louis Encephalitis from Culex Tarsalis Mosquitoes, Science **94**:328-330 (Oct. 3) 1941.

159. Blattner, R. J., and Heys, F. M.: Experimental Transmission of St. Louis Encephalitis to White Swiss Mice by Dermacentor Variabilis, Proc. Soc. Exper. Biol. & Med. **48**:707-710 (Dec.) 1941.

160. Wheeler, J. A.: Western Equine Encephalitis Occurring Among Human Beings in Kansas During the Summer of 1941, J. A. M. A. **117**:1972-1973 (Dec. 6) 1941.

161. Hammon, W. M.: Suggestions for the Possible Control of the American Summer Encephalitides, Correspondence, J. A. M. A. **118**:66-68 (Jan. 3) 1942.

they affect similar hosts and mosquitoes. They are probably impossible to control because of the widespread endemicity, and as in the case of plague, it may be better to learn to live with them than to fight them ineffectively. However, mosquito control, specific vaccination of human beings and horses, zoning restrictions and extermination of wild life (obviously impossible) may all help to reduce the incidence of the disease in human beings.

One might gather from tabular classifications that the problem of diagnosing encephalitis in human beings etiologically is relatively simple and that in most cases the disease falls into one of several well defined entities. That such is not the case is indicated in the previous paragraph and in the reports from several laboratories that in at least 80 per cent of cases encephalitis cannot be diagnosed etiologically by the methods available at present. Further evidence of the existence of at least one still unclassified form was presented by Price at the May meeting of the American Society of Clinical Investigation. Four cases of meningoencephalitis occurred almost simultaneously in a community. All tests applied to the blood and the spinal fluid failed to allow etiologic classification with the known forms.

Lymphocytic Choriomeningitis.—The subject was recently reviewed by Farmer and Janeway.[162] Milzer [163] transmitted lymphocytic choriomeningitis to guinea pigs by the mosquito Aedes aegypti but only at temperatures between 26 and 34 C. Transmission occurred from seven to thirty-eight days after the insect fed on an infected animal. The disease was also transmitted by bedbugs at temperatures between 22 and 25 C. Bedbugs are unable to transmit infection by biting alone. The virus is contained in the feces, which when rubbed into abrasions may cause infection. Mice and guinea pigs were also infected by swallowing infected mites. The virus persists through one or two larval stages.

Smadel and his associates [127] report 2 unusual fatal cases of lymphocytic choriomeningitis, with necropsy observations, as referred to on page 158.

Yellow Fever.—By the use of the mouse protection test, studies [164] in Africa show that yellow fever is spread much more widely than heretofore believed. Instead of being confined to the west coast alone, evidence of infection extends as far east as the Nile valley. The problem seems about as complex and extensive as in South America, where jungle yellow fever occurs throughout an enormous area. The problem

162. Farmer, T. W., and Janeway, C. A.: Infection with the Virus of Lymphocytic Choriomeningitis, Medicine **21**:1-64 (Feb.) 1942.

163. Milzer, A.: Studies on the Transmission of Lymphocytic Choriomeningitis Virus by Arthropods, J. Infect. Dis. **70**:152-172 (March-April) 1942.

164. Findlay, G. M.; Kirk, R., and MacCallum, F. O.: Yellow Fever and the Anglo-Egyptian Sudan: Distribution of Immune Bodies to Yellow Fever, Am. J. Trop. Med. **35**:121 (Dec. 31) 1941.

of transmission and of insect vectors in South America has recently been solved [165] by the discovery that a newly incriminated mosquito (Haemogamus) resides not necessarily near the surface of water and low lying ground but in tree tops. These mosquitoes unfortunately survive throughout the dry season and carry the causative virus over from one rainy season to the next and thus serve as a permanent reservoir. Jungle yellow fever frequently occurs in men engaged in felling trees.

Jaundice has occurred in a high percentage of soldiers several weeks to several months after vaccination against yellow fever. Whether the disease is a mild form of yellow fever has not been determined.

OTHER SPECIFIC INFECTIOUS DISEASES

Rickettsial Disease.—For years it was believed that the mortality rate from Rocky Mountain spotted fever was much greater in certain areas of the West than elsewhere in this country. Evidence now indicates this to be more apparent than real. In an epidemiologic study [166] the disease as it occurs in the eastern states was found to affect chiefly children, who are more exposed to ticks through recreational activities, and in the West men, whose occupations often favor exposure, are more often victims. Since the mortality rate from the disease is lower in children, the apparent difference in mortality rate is partly explained. When the fatality rates are corrected for age difference, they are about the same in both areas.

Further reasons may be found in the fact [167] that highly virulent strains of Rickettsia have been encountered in the East, and a strain of low virulence was found in the West, so that the terms eastern and western are no longer applicable. Designation at present is best made on the basis of virulence for guinea pigs.

Rocky Mountain spotted fever and typhus, usually thought to be caused by completely different or unrelated rickettsias, are, according to recent studies, not so different after all. Castaneda and Silva [168] demonstrated reciprocal cross immunity reactions between the rickettsias of both diseases, as I did in 1935 in studying a strain isolated in Minnesota which seemed to have characteristics of both varieties. This trend of thought is in line with evidence favoring a variety of similar strains among groups of infectious agents, such as the psittacine group of viruses and the influenza viruses.

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165. Fosdick, R. B.: The Rockefeller Foundation: A Review for 1941, New York, 1942, p. 13.

166. Topping, N. H.: Rocky Mountain Spotted Fever: A Note on Some Aspects of Its Epidemiology, Pub. Health Rep. **56**:1699-1703 (Aug. 22) 1941.

167. Topping, N. H.: A Strain of Rocky Mountain Spotted Fever Virus of Low Virulence Isolated in the Western United States, Pub. Health Rep. **56**:2041-2043 (Oct. 17) 1941.

168. Castaneda, M. R., and Silva, R.: Immunologic Relationship Between Spotted Fever and Exanthematic Typhus, J. Immunol. **42**:1-14 (Sept.) 1941.

It is still uncertain as to whether typhus in mice can be transformed into the historic epidemic variety by rat-man-louse-man passage. In China Liu and Zia [169] present evidence that the strain in mice may be transmitted from man to man by body lice and give rise to epidemics. The problem of typhus fever in China is summarized in a paper by Liu, Zia, Chung and Wang.[170] Brigham [171] isolated two strains of endemic typhus from chicken fleas removed from rats.

A suitable animal for the study of typhus fever was found in the cotton rat.[172] Complement fixation tests developed in two laboratories [173] proved useful in determining both recent and past rickettsial infection.

Ominous warnings as to the danger of new typhus epidemics in the war-ravaged areas of eastern Europe appear. The number of cases in Poland, Hungary and Bulgaria, for example, have doubled or trebled between 1940 and 1941.[174] With continued disorganization of millions of people and increasing hardship and starvation, the outlook for a large outbreak is grim indeed. To combat this pestilence large scale studies are being undertaken to test the prophylactic value of the new antityphus vaccine developed by Cox. Controlled experimental studies [175] were made by members of the National Institute of Health in a large group of South American Indians in an area where epidemic typhus is endemic. The report of results of this trial is anxiously awaited. In laboratories persons working with typhus material contracted the disease in spite of vaccination.

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169. Liu, W. T., and Zia, S. H.: Studies on Murine Origin of Typhus Epidemics in North China: I. Murine Typhus Rickettsia Isolated from Body Lice in Garments of Sporadic Case, Am. J. Trop. Med. **21**:507-524 (July) 1941.

170. Liu, W. T.; Zia, S. H.; Chung, H. L., and Wang, C. W.: Typhus Fever in Peiping, Epidemiologic Considerations, Am. J. Hyg. **35**:231-250 (March) 1942.

171. Brigham, G. D.: Two Strains of Endemic Typhus Fever Virus Isolated from Naturally Infected Chicken Fleas (Echidnophaga Gallinacea), Pub. Health Rep. **56**:1803-1804 (Sept. 5) 1941.

172. Snyder, J. C., and Anderson, C. R.: The Susceptibility of the Eastern Cotton Rat, Sigmodon Hispidus Hispidus to European Typhus, Science **95**:23 (Jan. 2) 1942.

173. Bengston, I. A.: The Specificity of the Complement Fixation Test in Endemic Typhus Using a Rickettsial Antigen, Pub. Health Rep. **56**:1723-1727 (Aug. 29) 1941. Plotz, H., and Wertman, K.: The Use of the Complement Fixation Test in Rocky Mountain Spotted Fever, Science **95**:441-442 (April 24) 1942.

174. Danger of a Typhus Epidemic in Europe. Statist. Bull. Metrop. Life Insur. Co. **22**:7-9 (Nov.) 1941.

175. New Typhus Vaccine Being Tested in Bolivia, Science **94**:340 (Oct. 10) 1941.

Further studies [176] are reported on the value of typhus antiserum prepared in rabbits with typhus rickettsias grown in yolk membranes from chick embryos. Administration to guinea pigs as late as five days after inoculation with typhus has a beneficial therapeutic effect.

Weil's Disease.—Thus far at least 20 definite cases and 20 presumptive cases of leptospirosis, or Weil's disease, have been reported in American literature. Larson [177] adds 51 more. Even these represent only a small portion of the actual number of cases. The diagnosis is often not made or not reported, especially in the mild forms and in those without jaundice. Forty per cent of the series of 51 cases occurred from June to August. Stiles and Sawyer [178] summarize recent knowledge of the infection and regard it as an occupational hazard.

Packchanian [179] calls attention to the value of the agglutination test in making diagnoses in cases of suspected leptospirosis, but for absolute diagnosis it is essential to isolate Leptospira icterohaemorrhagiae from the patient's blood or urine. This, of course, can only be accomplished early in the disease because Leptospira disappears from the blood after about five days and from the urine in a month. An interesting point in his study is the demonstration of strongly positive agglutination reactions on the serum of 20 jaundiced dogs from widely separated places in the United States.

According to Morton,[180] the Syrian hamster is a convenient and satisfactory animal to use for the diagnosis of leptospirosis. Other investigators have also shown the value of this animal for the diagnosis of influenza, St. Louis encephalitis, lymphocytic choriomeningitis, meningopneumonitis and lymphogranuloma venereum.

Rat Bite Fever.—Larson [181] reports 3 cases of rat bite fever, in 1 of which the disease was probably caused by Spirillum minus and in the others by Streptobacillus moniliformis, the same bacterium which causes Haverhill fever. Rat bite fever caused by both agents has also been

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176. Wyckoff, R. W. G., and Bohnel, E.: Therapeutic Effect in Guinea Pigs of Hyperimmune Epidemic Typhus Antiserum, Proc. Soc. Exper. Biol. & Med. **49**:712-715 (April) 1942.

177. Larson, C. L.: Weil's Disease: A Report of Fifty-One Cases Occurring in Puerto Rico and the United States, Pub. Health Rep. **56**:1650-1656 (Aug. 15) 1941.

178. Stiles, W. W., and Sawyer, W. A.: Leptospiral Infection (Weil's Disease) as an Occupational Hazard, J. A. M. A. **118**:34-38 (Jan. 3) 1942.

179. Packchanian, A.: Positive Agglutination Tests in Suspected Cases of Weil's Disease, Pub. Health Rep. **56**:2145-2156 (Nov. 7) 1941.

180. Morton, H. E.: Susceptibility of Syrian Hamsters to Leptospirosis, Proc. Soc. Exper. Biol. & Med. **49**:566-568 (April) 1942.

181. Larson, C. L.: Rat-Bite Fever in Washington, D. C., Due to Spirillum Minus and Streptobacillus Moniliformis, Pub. Health Rep. **56**:1961-1968 (Oct. 3) 1941.

noted in Illinois,[182] and that caused by S. moniliformis alone, in Virginia.[183] Apparently rat bite fever is composed of at least two etiologic entities. The subject is reviewed by Brown and Nunemaker,[184] who present convincing evidence that both agents may cause disease and that the S. moniliformis infection is the more common. Contrary to Klieneberger's view, there was consistent reversion between the micro-organisms causing pleuropneumonia and S. moniliformis. Klieneberger regarded them as different micro-organisms living in symbiosis, but it is most likely that bacterial dissociation accounts for the transformation of one form into the other.

Bacteria of the pleuropneumonia group were once regarded as a possible cause of rheumatic fever or rheumatoid arthritis because of the arthritis they cause in animals. According to Preston,[185] the arthritis in animals is of the suppurative type and bears little resemblance to the disease in human beings.

Cases of relapsing fever and instances of ticks carrying the infection were reported from Oregon [186] and from Utah. The infection exists in most of the western states.

Welt [187] found that trichinosis could be induced in monkeys by feeding them one Trichina larva per gram of body weight. Fever, edema and eosinophilia developed. Antibodies, as demonstrated by the precipitin test, developed in the serum and in the urine after several weeks. The cutaneous test also may be valuable in diagnosis.

Pork infected with Trichina can be made safe for human consumption by proper freezing.[188] For example, the parasites may be killed by refrigeration of sections of pork not more than 6 inches (15 cm.) thick at 5 F. for twenty days. Lower temperatures require shorter exposure.

Malaria.—A causal relation between ferrihemate, the pigment liberated by sporulating parasites of malaria, and the paroxysm of the

182. Kirkwood, T., and Stoll, C. G.: Rat-Bite and Haverhill Fevers, Illinois M. J. **80**:141-144 (Aug.) 1941.

183. Hart, A. D.: Haverhill Fever Following Rat Bite, Virginia M. Monthly **68**:582-584 (Oct.) 1941.

184. Brown, T. M., and Nunemaker, J. C.: Rat-Bite Fever: A Review of the American Cases with Reevaluation of Etiology; Report of Cases, Bull. Johns Hopkins Hosp. **70**:201-328 (March) 1942.

185. Preston, W. S.: Arthritis in Rats Caused by Pleuropneumonia-Like Micro-Organisms and the Relationship of Similar Organisms to Human Rheumatism, J. Infect. Dis. **70**:180-184 (March-April) 1942.

186. Davis, G. E.: Ornithodoros Hermsi and Relapsing Fever in Oregon, Pub. Health Rep. **56**:2010-2012 (Oct. 10) 1941; Ornithodoros Parkeri and Relapsing Fever Spirochetes in Utah, ibid. **56**:2464-2468 (Dec. 26) 1941.

187. Welt, L. G.: Urinary Excretion of Trichina Antigen in Experimental Trichinosis, Proc. Soc. Exper. Biol. & Med. **48**:587-589 (Dec.) 1941.

188. Items, Science (supp.) **95**:14 (March 20) 1942.

disease has been suggested,[189] because of a similar reaction produced by the injection of ferrihemate solution in animals. It was shown, however, that the pigment is not liberated in soluble form from the plasmodia and is therefore not the cause of the paroxysm.

By using Plasmodium knowlesi antigen–coated collodion particles, according to Goodner's method, or by addition of collodion particles at the time of combining antigen and antibody, specific precipitin reactions in malaria in human beings were demonstrated by microscopic agglutination.[190] The test may prove to be of value in diagnosis.

Fungous and Yeast Infections.—An interesting group of cases of sporotrichosis among florists was described.[191] All patients had handled sphagnum moss and the flat fern, and all had had previous wounds of the skin. In a paper[192] entitled "Torula Infection of the Lungs and Central Nervous System," the lungs were scarcely mentioned in the 6 case reports. The description dealt chiefly with involvement of the central nervous system.

In a paper[193] describing an unusual case of endocarditis caused by a fungus, Candida parakrusei, in a habitual user of diacetylmorphine (heroin) the authors refer to 5 other cases of endocarditis of similar origin, all occurring in drug addicts. They feel that fungi isolated in cases of mycotic infection are often considered to be contaminants and are discarded as such, when actually they are the cause. In the case described the diacetylmorphine used was not found to contain spores of the fungus, but other samples may have been contaminated and may have accounted for the infection of the other addicts within the past two years. Another possible source of infection, of course, is the skin.

A case of histoplasmosis was reported from Brazil,[194] 1 from Michigan[195] and another from Illinois.[196] In the last-named case a

189. Morrison, D. B., and Anderson, W. A. D.: On the Role of Parasite Pigment in the Malaria Paroxysm, Pub. Health Rep. **57**:161-174 (Jan. 30) 1942.

190. Dulaney, A. D., and House, V.: Precipitative Tests in Malaria, Proc. Soc. Exper. Biol. & Med. **48**:620-623 (Dec.) 1941.

191. Gastineau, F. M.; Spolyar, S. W., and Haynes, E.: Sporotrichosis: Report of Six Cases Among Florists, J. A. M. A. **117**:1074-1077 (Sept. 27) 1941.

192. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System: Report of Six Cases with Three Autopsies, Arch. Int. Med. **68**:57-79 (July) 1941.

193. Wikler, A.; Williams, E. G.; Douglass, E. D.; Emmons, C. W., and Dunn, R. C.: Mycotic Endocarditis: Report of a Case, J. A. M. A. **119**:333-336 (May 23) 1942.

194. Villela, E., and Madureira Para: Histoplasmosis in Child, Rev. brasil. de biol. **1**:449 (Dec.) 1941.

195. Ramsey, T. L., and Applebaum, A. A.: Histoplasmosis "Darling," Am. J. Clin. Path. **12**:85-94 (Feb.) 1942.

196. Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Specific Cutaneous Reactions with Histoplasmosis: Preliminary Report of Another Case, J. A. M. A. **117**:436-437 (Aug. 9) 1941.

cutaneous test made with a filtrate of a culture of the causative fungus gave a specific reaction. Such a test may possibly serve as a helpful diagnostic aid. Histoplasmosis as a cause of ulcerative disease of the colon [197] is discussed on page 172.

Editorial comment [198] on histoplasmosis briefly summarizes the subject and states that thus far the disease has been invariably fatal. One wonders whether this is actually so or whether the diagnosis is not made in cases of mild forms with recovery, as was once the case with coccidioidomycosis, as discussed in the next paragraph.

Coccidioidomycosis.—Only a few years ago coccidioidomycosis was diagnosed only in its most severe form as coccidioidal granuloma and was regarded as a disease of high mortality. Since the recognition of the mild forms of the infection, the concept of the disease has changed. It is actually a common disease in some localities, manifesting itself in most instances as a subclinical or an inapparent infection or as a minor infection of the respiratory tract, most often mistaken for the common cold or for influenza. In rare instances the chronic form may be characterized by persistent suppurative arthritis, with Coccidioides immitis easily demonstrable in the pus.[199] The severe, often fatal, forms with multiple granulomatous lesions or erythema nodosum are fortunately rare. In Smith's [200] experience coccidioidomycosis in endemic centers like the San Joaquin Valley in California is almost always mild and is mistaken for influenza, pneumonia, poliomyelitis or typhoid fever. It is thought that eventually most inhabitants of the region contract the infection. According to Winn,[201] 76 to 84 per cent of patients show a positive cutaneous reaction to injected coccidioidin. Similar views are expressed by Davis, Smith and Smith,[202] who report a small outbreak affecting 7 to 14 members of a party on a field trip who were probably infected by inhaling spore-laden dust. The victims became sick nine to fourteen days later.

197. Henderson, R. G.; Pinkerton, H., and Moore, L. T.: Histoplasma Capsulatum as a Cause of Chronic Ulcerative Enteritis, J. A. M. A. **118**:885-889 (March 14) 1942.

198. Histoplasmosis, editorial, J. A. M. A. **119**:265-266 (May 16) 1942.

199. Rosenberg, E. F.; Dockerty, M. B., and Meyerding, H. W.: Coccidioidal Arthritis: Report of a Case in Which Ankles Were Involved and Condition Was Unaffected by Sulfanilamide and Roentgentherapy, Arch. Int. Med. **69**:238-250 (Feb.) 1942.

200. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health **30**:600-618 (June) 1940.

201. Winn, W. A.: Pulmonary Cavitation Associated with Coccidioidal Infection, Arch. Int. Med. **68**:1179-1214 (Dec.) 1941.

202. Davis, B. L.; Smith, R. T., and Smith, C. E.: An Epidemic of Coccidioidal Infection (Coccidioidomycosis), J. A. M. A. **118**:1182-1186 (April 4) 1942.

Roentgenographic studies [203] on these patients showed numerous diffuse patchy areas of infiltration which may be mistaken for "virus" pneumonia. Loeffler's pneumonia might be thought of because of the eosinophilia. Cavitation, which occurred in many involved areas, may seriously confuse the diagnosis with pulmonary tuberculosis unless etiologic studies are made. Diagnosis is made by the history of the illness, the location where the disease was contracted, the presence of double contoured spherules in the sputum, a positive reaction to coccidioidin, animal inoculation, agglutination and precipitin tests, leukocytosis with eosinophilia and patchy areas of density in the lungs with cavitation. In cases of the severe form chronic granulomatous lesions of the skin and erythema nodosum occur.

Shelton [204] tested nearly 900 soldiers in a camp in California with coccidioidin and found 14 to have acquired specific hypersensitivity during a three month period. Several cases of clinical coccidioidomycosis occurred in this camp, which is located in an area not previously known as an endemic focus.

In studies [205] made elsewhere to determine the source of infection, the fungus Coccidioides was cultivated directly from desert soil. Small rodents apparently may harbor the fungus and in turn contaminate the soil; the spores then become suspended in dust and air and are inhaled by man. In another study in Arizona, 25 of 105 small wild rodents harbored fungi, of which three were species of Coccidioides.

MISCELLANEOUS DISEASES

Several studies on the etiology of chronic ulcerative colitis were published. Acute and chronic enteritis, including ulceration of the mucosa of the colon, was produced in dogs by obstructing the lymphatic drainage of the ileocecal segment of intestine.[206] The presence of mesenteric lymphatic obstruction is sufficient to produce ulceration of the rectal mucosa without the agency of bacteria. These studies support the view that the disease may be initiated by noninfectious factors. Others [207] summarized the evidence implicating Bacterium necrophorum as the cause. It seems that this bacterium may predominate over others in the colon in some cases; it has been found in most cases and specific

203. Powers, R. A., and Starks, D. J.: Acute (Primary) Coccidiomycosis: Roentgen Findings in a Group Epidemic, Radiology **37**:448-453 (Oct.) 1941.

204. Shelton, R. M.: A Survey of Coccidioidomycosis at Camp Robert, California, J. A. M. A. **118**:1186-1190 (April 4) 1942.

205. Emmons, C. W.: Isolation of Coccidioides from Soil and Rodents, Pub. Health Rep. **57**:109-111 (Jan. 23) 1942.

206. Poppe, J. K.: Reproduction of Ulcerative Colitis in Dogs, Arch. Surg. **43**: 551-558 (Oct.) 1941.

207. Dragstedt, L. R.; Dack, G. M., and Kirsner, J. B.: Chronic Ulcerative Colitis: Summary of Evidence Implicating Bacterium Necrophorum as Etiologic Agent, Ann. Surg. **114**:653-662 (Oct.) 1941.

antibodies against it appear in the blood. The evidence presented thus far as to its etiologic relation to the disease is not particularly convincing. It is still uncertain whether this micro-organism, like Vincent's spirillum, is merely a saprophyte which thrives in tissue made necrotic by other causes.

Of interest is the report [197] of a case in which Histoplasma capsulatum was found in intestinal ulcers, the mesenteric lymph nodes and elsewhere and was apparently the cause of prolonged diarrhea. In a review of 25 previously reported cases of histoplasmosis the authors stated that similar lesions occurred in the intestine in 8 cases but in only 2 was there prolonged diarrhea. It would appear, as many investigators have already suggested, that chronic ulcerative colitis is a syndrome resulting from a variety of causes both infectious and noninfectious.

A peculiar "new" form of epidemic infectious conjunctivitis caused a perplexing problem in Hawaii in the summer of 1941.[208] The infection apparently entered California in the autumn. The cause has not been determined but is believed to be a filtrable virus. Infection seems to take place by contact, and after an incubation period of two to five days severe conjunctivitis occurs. The disease is self limiting and lasts from two to three weeks. No specific form of treatment is known.

Nettleship [209] inoculated the chorioallantoic membrane of chick embryos with filtered nasal washings from 8 patients with infectious mononucleosis and obtained positive results in 4 instances in the form of ectodermal proliferation and heavy monocytic cell infiltration. The reaction could be continued through four to fourteen passages but eventually disappeared. Attempts at animal transmission were unsuccessful.

Newman [210] had the unusual opportunity of studying an outbreak of infectious, or catarrhal, jaundice in a community. As the only physician in charge, he was able to observe all illnesses continuously and thus to correlate typical with atypical cases. The epidemic appeared at intervals in small series of cases and extended from January to April, involving 33 patients. Person to person contact seemed essential, and its spread by droplet infection seemed probable. Of importance was the occurrence of many cases of a mild form of apparently the same disease, but without jaundice, which no doubt would not have been associated with the epidemic had not a single physician observed all cases. In these atypical cases the condition could have been mistaken for meningitis, grip or appendicitis had they occurred as isolated instances.

208. Holmes, W. J.: Epidemic Infectious Conjunctivities, Hawaii M. J. **1**:11-12 (Nov.) 1941.

209. Nettleship, A.: On Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **49**:116-117 (Feb.) 1942.

210. Newman, J. L.: Infective Hepatitis: The History of an Outbreak in the Lavant Valley, Brit. M. J. **1**:61-65 (Jan. 17) 1942.

A phytopathogenic bacterium discovered recently [211] as the cause of bacterial leaf spot of tobacco is highly virulent for rabbits, guinea pigs and mice, causing septicemia and death. Its ability to multiply in animals and plants is remarkable and is interesting from an evolutionary point of view. It is perhaps the first micro-organism discovered which is pathogenic both for plants and for animals.

DISINFECTION OF AIR

Wells, Wells and Wilder [212] report further study of the effects of radiant disinfection of air as a method to prevent the spread of contagious disease. The results were gratifying in that no contagious disease occurred among children in irradiated groups in two schools, while measles and mumps occurred among the controls. The primary object was not to postpone contagious diseases to later childhood, though this may at times be desirable, but to test the hypothesis that contagion may be controlled by irradiation, as in army barracks and among groups in which immediate protection against disease may be imperative.

Buchbinder [213] reviews modern work showing how important airborne infection is and that the old "contact" theory of spread of infection is not adequate. He points out the germicidal effectiveness of sunlight and even of diffuse daylight.

The importance of stirring up dust and the resuspension of bacteria in air as an important source of infection are emphasized, especially when hemolytic streptococci are involved. One may point out how little attention has been paid to air-borne infection in operating room technic, yet it is surprising how few infections occur even during operations performed in an open room with 100 or more students scuffling about and raising dust. It has always seemed to me that "sterile technic" in operating rooms is greatly exaggerated and that thousands of dollars might be saved if unnecessary procedures were eliminated by some one with courage to show the way. Much may be learned in this respect from surgery in wartime conditions.

The author discusses chemical sprays as air disinfectants, such as hexylresorcinol, a solution of resorcinol in glycerin, organic smokes, sodium hypochlorite solution, propylene glycol, ethylene glycol and trimethylene glycol. He states that Twort has listed the first four in decreasing order of effectiveness. The possible injurious effect of aerosols on experimental subjects exposed to them over long periods is as yet unknown.

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211. Elrod, R. P., and Braun, A. C.: A Phytopathogenic Bacterium Fatal to Laboratory Animals, Science **94**:520-521 (Nov. 28) 1941.

212. Wells, W. F.; Wells, M. W., and Wilder, T. S.: The Environmental Control of Epidemic Contagion: An Epidemiologic Study of Radiant Disinfection of Air in Day Schools, Am. J. Hyg. **35**:97-121 (Jan.) 1942.

213. Buchbinder, L.: The Transmission of Certain Infections of Respiratory Origin: A Critical Review, J. A. M. A. **118**:718-730 (Feb. 28) 1942.

As little as 1 Gm. of propylene glycol in 2,000,000 to 4,000,000 cc. of air is bactericidal for pneumococci, streptococci, staphylococci, H. influenzae and other bacteria.[213a]

In another[214] practical application of prophylaxis against air-borne infection, air conditioning alone failed to prevent acute cross infections of the respiratory tract in infants, but air conditioning together with germicidal light barriers or with mechanical barriers was effective. Numerous other reports of favorable results of the use of germicidal light are referred to in this paper.

ANTIBIOTIC AGENTS

The subject of antibiotic agents has been reviewed by Waksman.[215] Since then other papers have appeared.

According to Rammelkamp,[216] different strains of staphylococci vary in their susceptibility to the action of tyrothricin, which together with the irregular development of resistance to the substance probably accounts for the different results obtained in treating patients with staphylococcic infections with this substance. Staphylococci grown in vitro are able to establish increasing resistances to the inhibitory and bacterial action of tyrothricin. Tyrothricin has no effect on Lactobacillus acidophilus in the intestines of mice when given orally.[217] Besides bacteriostatic and bactericidal activity, both tyrothricin and actinomycin A, a substance isolated from Actinomyces antibioticus, inhibit fibrinolysis by hemolytic streptococci and interfere with the coagulation of plasma by staphylococci.[218]

Bacteriologic culture medium containing tyrothricin is claimed to be helpful in isolating Haemophilus influenzae by inhibiting the growth of other bacteria.[219]

213a. Robertson, O. H.; Bigg, E.; Puck, T. T., and Miller, B. F.: Bactericidal Action of Propylene Glycol Vapor on Microorganisms Suspended in Air, J. Exper. Med. **75**:543-609 (June) 1942.

214. Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Control of Cross Infections of the Respiratory Tract in a Nursery for Young Infants: A Preliminary Report, J. A. M. A. **118**:1271-1274 (April 11) 1942.

215. Waksman, S. A.: Antagonistic Relations of Microorganism, Bact. Rev. **5**: 231-291 (Sept.) 1941.

216. Rammelkamp, C. H.: Observations on the Resistance of Staphylococcus Aureus to Action of Tyrothricin, Proc. Soc. Exper. Biol. & Med. **49**:346-350 (March) 1942.

217. Weinstein, L., and Rammelkamp, C. H.: A Study of the Effect of Gramicidin Administered by the Oral Route, Proc. Soc. Exper. Biol. & Med. **48**: 147-149 (Oct.) 1941.

218. Neter, E.: Effects of Tyrothricin and Actinomycin A upon Bacterial Fibrinolysis and Plasma-Coagulation, Proc. Soc. Exper. Biol. & Med. **49**:163-167 (Feb.) 1942.

219. Schoenbach, E. B., and Seidman, L. R.: A Selective Medium for Isolation of Hemophilus Influenzae, Proc. Soc. Exper. Biol. & Med. **49**:108-110 (Jan.) 1942.

A new substance, streptothricin, isolated from a soil Actinomyces, has been found to inhibit the growth of gram-negative bacteria like Escherichia coli and of gram-positive ones like Bacillus subtilis and micrococci.[220] It also is bactericidal for gram-negative bacteria.

In therapeutic trials [221] in 12 cases of various types of infection tyrothricin apparently caused local beneficial effects in 6 and was of doubtful value in the rest. In cases like these it is not always easy to provide adequate controls. In a further study [222] on more patients the same authors report that of 50 cases, the results were good in less than half, fair in 25 per cent and poor in 32 per cent.

English investigators [223] report further studies on penicillin, a similar antibiotic agent produced by the mold Penicillium. They describe the technic for its isolation and preparation for clinical use. In test tube experiments the bacteriostatic effect of penicillin on streptococci and staphylococci was greater than that of sulfanilamide compounds. Penicillin unlike the drugs was not antagonized by pus when applied to wounds. It had no harmful effect on leukocytes. In clinical trials both by intravenous injection and by local application the authors report favorable effects, but many more studies are necessary to determine the actual value of penicillin as a therapeutic agent and its possible harmful side effects.

Immune Reactions.—When normal globulin or other protein is subjected to the action of denaturing reagents or conditions in the presence of an antigen, the protein molecule unfolds and then refolds in such a way as to acquire the properties of a specific homologous antibody. In this ingenious manner Pauling and Campbell [224] have for the first time been able to produce specific antibodies in vitro.

Although fever has long been regarded as an attempt on the part of the body to combat infection and has led to the use of artificially induced fever as a method of treating certain infectious diseases, Ellingson and Clark [225] now show that hyperpyrexia causes a significant lowering of

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220. Waksman, S. A., and Woodruff, H. B.: Streptothricin, a New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **49**:207-210 (Feb.) 1942.

221. Herrell, W. E., and Heilman, D.: Experimental and Clinical Studies on Gramicidin, J. Clin. Investigation **20**:583-591 (Sept.) 1941.

222. Herrell, W. E., and Heilman, D.: Further Experimental and Clinical Studies on Gramicidin, J. A. M. A. **118**:1401-1402 (April 18) 1942.

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the specific antibody titer and perhaps actual destruction of antibodies in experimental animals. In spite of this untoward evidence, the effect of temperature at fever levels on the destruction of certain bacteria, the increase in the circulation of blood, the changes in the viscosity of blood, the increased activity of phagocytes and other factors still indicate the value of fever in combating infections. There is, of course, a great difference in the effect of "genuine" fever as the result of infection or the presence of foreign protein in the body as compared with that of fever produced by heating the body artificially or by raising the temperature by preventing radiation of normally produced heat. Fever caused by infection makes far more profound changes in the body than the mere elevation of temperature by other processes.

Goodner [226] has devised a supersensitive specific immunologic test employing the principle of collodion fixation. The test is reported to be about a thousand times more delicate than any heretofore described immune reaction and may eventually be of value in the identification of filtrable viruses.

Tsao [227] showed that the administration of estrogens from the urine of pregnant women increased and maintained the bactericidal property of the blood serum of adult male rabbits against Eberthella typhi as long as three hundred days. It was not determined if this effect was a direct response to the estrogen or was due to changes in the body.

Freeman [228] investigated a peculiar phenomenon concerning the lack of immunity of mice to a latent virus, habitually carried by them. The host-virus relation seemed to be stable until disturbed by some procedure which reduced resistance. The virus then became invasive, killing all the mice that became sick. Mice inoculated deliberately with the virus and some inoculated intranasally with sterile physiologic solution of sodium chloride became sick, but on retest they were all again susceptible to infection. Uninoculated cagemates of sick and moribund mice did not contract the disease and were not immune. Immune serum prepared in rabbits failed to protect against infection. These apparent paradoxic facts seem to parallel certain observations on human beings, particularly in studies on herpes simplex or on influenza in which demonstrable immune bodies do not seem to protect certain patients from infection.

Jefferson Medical College.

226. Goodner, K.: Collodion Fixation: A New Immunological Reaction, Science **94**:241-242 (Sept. 5) 1941.

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News and Comment

American College of Physicians.—The American College of Physicians will hold its twenty-seventh annual session in Philadelphia, April 13 to 16, inclusive, 1943. In the interest of conserving time and money for members, the program will be condensed into four days, Tuesday through Friday, instead of extending over the usual five days. Dr. James E. Paullin, Atlanta, Ga., president, will have charge of the general sessions and lectures; Dr. George Morris Piersol, Philadelphia, general chairman, will be responsible for the hospital clinics, panel discussions, local arrangements and entertainment, and the general management of the session and the technical exhibits will be handled by the executive secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia.

Other medical societies are urged to avoid conflicting dates for mutual benefit.

American Association for the Advancement of Oral Diagnosis.—The ninth annual congress of the American Association for the Advancement of Oral Diagnosis will be held in Boston November 12 and 13 at the Forsyth Dental Infirmary.

The subject of this year's congress will be "The Military Aspects of Oral Diagnosis."

Members of the medical and the dental profession in the United States and the countries of the Western Hemisphere who are interested are cordially invited to attend and may obtain programs by communicating with the secretary, H. Justin Ross, 515 Madison Avenue, New York.

Chicago Society of Internal Medicine.—At the annual meeting of the Chicago Society of Internal Medicine, held May 25, 1942, the following officers were elected: LeRoy H. Sloan, president; Italo F. Volini, vice president; Richard B. Capps, secretary-treasurer, and Howard L. Alt, secretary-treasurer pro tem.

Book Reviews

Psychosurgery: Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders. By Walter Freeman, M.D., Professor of Neurology, and James W. Watts, M.D., Assistant Clinical Professor of Neurosurgery, George Washington University. Price, $6. Pp. 338, with 81 figures. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

This is one of the most interesting and important books of the year because it marks the first major development in the treatment of mental disease since the advent of shock therapy. A new operation for certain types of psychoses and neuroses is described in minute detail in part III. Briefly, the procedure consists in making a burr hole in the skull over the premotor area of the frontal lobe. A flat blade shaped like a spatula is inserted 5 cm. into the brain and given a pendulum-like movement, so that it severs most of the fiber tracks which traverse the white matter at this level. The operation is performed on both sides at one sitting. The net result is a partial but permanent separation of the frontal lobes from the rest of the brain. An operation of this type was first performed in 1935 by Egas Moniz, to whom the book is dedicated. The authors report their experience with a modified operation in 80 consecutive cases of mental disorder.

Although the authors concede that the frontal lobes are essential for satisfactory social adaptation, they suggest that mental disorder may be due to perverted activity of these lobes and that therefore a person may become better adapted if the lobes are partially inactivated. The obvious corollary is that without the frontal lobes there could be no functional psychosis. Specifically, the partial separation of the frontal lobes from the rest of the brain results in reduction of disagreeable self consciousness, abolition of obsessive thinking and satisfaction with performance, even though the performance is inferior in quality. The emotional nucleus of the disorder is said to be removed. Even though fixed ideas may persist and compulsion may continue for a while, the fear that disabled the patient is banished. The authors find that the relief to those persons suffering from doubts, fears, morbid thoughts, hallucinations, delusions and compulsive activities is great.

The operation is reserved for those patients whose outlook is poor, whose response to other treatment is poor and for those who are approaching disability or suicide.

Thirty-eight of the 80 patients were suffering from involutional depression. Twelve had schizophrenia, and 4 had unclassified psychoses. Nineteen other patients were classified as having obsessive-compulsive neuroses and obsessive-ruminative tension states. The remaining 7 had miscellaneous neuroses. Part IV of the book, which deals with a careful analysis of all the cases, can be briefly summarized by saying that in 50 cases the results were satisfactory, in 16 cases they were fair, in 11 cases they were bad and in 3 cases death resulted.

Part II is valuable in itself as a critical analysis of modern knowledge of frontal lobe function. Parts I and V deal with the historical background and the psychopathologic aspects of the study of prefrontal lobotomy.

Whether or not prefrontal lobotomy becomes a universally accepted treatment for mental disorders cannot safely be speculated about for some years to come. Nevertheless, the study of the patients who have already been operated on has contributed tremendously toward the understanding of pathologic mental processes. This book will be enjoyed by every one who has any interest in mental disorders.

The Pharmacology of Anesthetic Drugs. By John Adriani, M.D., Instructor in Anesthesia, New York University College of Medicine, Assistant Visiting Anesthetist, Bellevue Hospital. Price, $3.50. Pp. 86. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This syllabus is obviously a teaching aid and should therefore be evaluated on the basis of experience with it in the training of anesthetists rather than on the impressions obtained by a pharmacologist from a casual perusal. According to the author, the outline is limited to fundamentals and is intended "to acquaint the student anesthetist . . . with pharmacological facts relating to drugs in current use." The amount of information available in this book relating to the pharmacology of volatile and of nonvolatile anesthetics, barbiturates, opium and opium derivatives, atropine, analeptics and nonanesthetic gases, such as oxygen and carbon dioxide, is considerable. Although of necessity dogmatically given, the views are those generally accepted in pharmacologic circles. Certainly no student of anesthesia who has assimilated any considerable part of the information here presented can use these agents without thinking in terms of physiologic mechanisms.

This reviewer has but two criticisms to offer. At times some of the information presented, important as it may be, seems to him to be somewhat beyond the experience and training of those persons for whom the manual is intended. An example is the discussion of the modification of the pharmacology of morphine by alteration of the hydroxyl groups, as by methylation or acetylation. The same criticism might be made of the presentation of the chemistry of atropine and its relatives or of the pharmacology of parasympathetic action. A second criticism, also not too important, has to do with the general form in which the material is presented. Extensive use is made of conventionalized diagrams. For example, on many pages there is a human figure in outline with certain structures indicated diagrammatically—stomach, colon, liver, bladder, etc. The facts regarding the actions of the drug under discussion are condensed into small paragraphs on the margins of the page, with dotted lines to those parts of the body involved. Even though this book is a syllabus, this procedure seems rather elementary, considering the nature of the material involved, and in some cases it leads to what are essentially inaccuracies of fact. For example, under "Atropine, lungs" occurs the comment "oxygen consumption increased," with a dotted line to the lungs.

The volume is attractively arranged and printed. There are a fairly extensive bibliography and a complete index.

Breathing Capacity and Grip Strength of Preschool Children. By Eleanor Metheny, Ph.D. University of Iowa Studies: Studies in Child Welfare, volume 18, number 2. Price, $1.35, paper, and $1.70, cloth. Pp. 207, with illustrations. Iowa City: University of Iowa, 1940.

This book relates the experiments of Dr. Metheny on breathing capacity and grip strength. The study is divided into four sections, namely, (1) Problem and Data, (2) Breathing Capacity, (3) Grip Strength and (4) Health Relationships. Each of these sections is fully discussed, with excellent charts and illustrations. At the close of each section is a complete summary. Dr. Metheny describes some new designs for the spirometer and the dynamometer which permit high reliability in measurements.

Grip strength and breathing capacity determinations were done on some 169 children from 2½ to 6 years of age. The results of these tests were analyzed in relation to anthropometric measurements. The grip strength was found superior in girls. No difference was noted when children were compared from the social and the mental standpoint.

Dr. Metheny's work does suggest that prior to the onset of a cold there is a decrease in strength and breathing capacity. If this is so, which does require further proof, it may prove a valuable contribution.

At the close of this book is a list of one hundred and thirty-one references.

The book should serve as a valuable reference guide on this important subject, namely, breathing capacity and grip strength of the preschool child, also for other age groups.

The Lymphatic System, Its Part in Regulating Composition and Volume of Tissue Fluid: The Lane Medical Lectures. By Cecil K. Drinker, M.D. Price, $2.25, cloth, $1.50, paper. Pp. 101, with illustrations. Stanford University P. O., Calif: Stanford University Press, 1942.

This group of the Lane Medical Lectures continues the high quality of the former ones. The lectures are divided into five parts, "Physiological Principles Displayed in the Evolution of the Mammalian Circulation," "Establishment and Characteristics of the Capillary Circulation," "Appearance and Elaboration of Lymphatic Vessels," "Blood, Tissue Fluid and Lymph, as Illustrated by Experiments Upon the Heart and Lungs" and "Relations of the Lymphatic System to Practical Problems in Surgery and Medicine."

The material is delightfully presented, with the important data condensed in a few pages. Many contributions of historical significance are included in the discussions. There are many interesting illustrations and a fairly good bibliography. The fifth portion of the lectures is of practical value to all clinicians. The first part of the lectures is of interest to students of circulatory phenomena as well as to clinicians. The reviewer only regrets that he was not present to hear the lectures presented by Dr. Drinker, who has made many important contributions to the understanding of the functions of the lymphatics.

Annual Review of Physiology. By James Murray Luck and Victor E. Hall. Vol. IV. Pp. 709. Stanford University P. O., Calif.: American Physiological Society and Annual Reviews, Inc., 1942.

It is difficult to imagine any physician so industrious as to be able adequately to keep up with all the advances which are made in medical science each year, no matter how systematically he uses his time. This is true of each branch of medicine, but especially true of internal medicine. Much of an internist's daily work is concerned with normal physiologic function and with deviations from normal function. Hence, a volume which furnishes him with a critical summary of a year's work in this field is especially welcome and fills a definite need.

The present volume is edited by a committee of the American Physiological Society, composed of men who are especially well qualified to select those contributions worthy of comment and to prepare each of the twenty-three sections devoted to particular fields of physiology. The bibliographic references are complete, and there are adequate author and subject indexes. The volume is practically indispensable for those persons interested in internal medicine and its advances.

Tumores primitivos malignos bronco-pulmonares. By Julio Palacio and Egidio S. Mazzei. Pp. 341, with 129 illustrations. Buenos Aires: El Ateneo, 1940.

This monograph can be said to be one of the most excellent pieces of work ever written on that particular subject.

It is divided into three main parts: (*a*) bronchopulmonary carcinomas, (*b*) sarcomas and (*c*) pulmonary lymphogranulomatous lesions.

The first division takes up almost the whole volume and is really the part the brilliance of which makes the monograph outstanding.

The subject has been presented with complete thoroughness from the point of view of diagnosis, and the illustrations are numerous and well chosen; several colored plates add to the understanding of the text. Little is said as to treatment, and the only opinion expressed is that the present forms of therapy serve more as means of prolonging life, since the proportion of cures is so small. Of particular note is the bibliography, which is complete and represents a great deal of work.

Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation. By Bernhard Zondek. Price, $4.50. Pp. xxiv + 264, with illustrations. New York: Williams & Wilkins Company, 1941.

This monograph, a valuable contribution by an outstanding investigator and clinician, contains a summary of the author's clinical and experimental investigations, together with a résumé of the most important work on the endocrine aspects carried on by other investigators. The text is well written, and the illustrations are excellent. The material contained in this volume is authentic, exhaustive and especially interesting to clinicians, endocrinologists, physiologists and research workers. This volume is heartily recommended to any one interested in the field of endocrinology.

La protidemia: su valor clinico. By Aron Gorodner. Thesis. Pp. 143. Buenos Aires: Aniceto Lopez, 1941.

The author has determined the albumin and globulin content of the blood serum in a number of patients suffering from a variety of diseases. The data he presents are limited in value because factors affecting the level of the blood proteins are many; the author considers only one, the disease per se, without regard for its severity, duration or complications. It seems to the reviewer that the chief purpose of the thesis has been achieved in its compilation: The author has learned much about the blood proteins and has demonstrated that knowledge to the satisfaction of his faculty.

Trastornos cardiacos en los estados anemicos. By Eugenio R. Pietrafesa. Pp. 209, with 127 illustrations. Buenos Aires: El Ateneo, 1941.

Clinical observations and comprehensive research on rabbits are the basis of this study of the cardiac conditions seen frequently in patients with anemia.

Nothing new is added to what is already known in the correction of these conditions.

The arrangement of the material makes reading somewhat difficult and uninteresting.

Wounds and Fractures. By H. Winnett Orr. Price, $5. Pp. 270, with 137 figures. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This book seems especially suitable for general practitioners or surgeons, since it takes up the subject not only by general discussion but by means of many case histories amplified by excellent illustrations. The material is well arranged and should be especially useful today when wounds in combat or civilian injuries may be encountered at any time.